Thyroid FNA: Diagnosis, Challenges and Solutions

Zubair W. Baloch, MD, PhD

Disclosures

• None
Questions to Myself?

Where We are Now?

The Present
**Reality Check**

**There is More to How Thyroid Nodules are Managed Then Just FNA and Cytologic Diagnosis**

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**Let’s Make Sense of Present**

&

**Predict Future**

**In Light of Past**
Thyroid Nodule Management Paradigms
Aka
Personalized Approach

Clinical Presentation
+ Ultrasound
+ FNA Diagnosis
+ Molecular Testing

A Diagnostic Thyroid FNA Specimen

Considerations
Specimen Adequacy

Major Problems: Specimen Adequacy

- Poor sampling and preparation
  - Poor localization
  - Faulty technique
  - Inexperience
- Cystic lesion
- Calcification and fibrosis
- Previous FNA
Non-Diagnostic
I did 12-passes
Look at the slides again

Problems: Cyto-preparations
Problems: Preparation and Fixation

- Poor smearing
- Fixation artifact
- Local anesthesia
- Air drying

Thyroid FNA Adequacy

- Abundant colloid and macrophages not adequate

- Representative, well preserved, follicular cells essential – *single most important factor*
  - 6 groups of cells with 10-20 cells each on two slides
  (Goellner 1987)
When Thyroid FNA Specimen is Adequate?

- A sample is adequate when:
  - It shows a pathologic process
  - But when the sample appears “benign”?
    - Is it safe to exclude malignancy?

Epithelial Quantitation

- Most commonly employed criterion:
  
  “at least 6 groups of benign follicular cells are required, each group composed of at least 10-20 cells.”
Thyroid Cysts

• True (pure) cysts are rare
  – 4% of thyroid “cysts” are true cysts

• Most thyroid nodules are complex
  – Mixed cystic and solid components
    • 30% of palpable thyroid masses
    • 50% of ultrasound detected nodules
  – Complex thyroid nodules:
    • Risk of malignancy 5 to 37% (estimated mean 15%)
      – Majority are papillary carcinomas

• FNA from thyroid “cysts” have a high rate of inadequacy
  – Often lack epithelial cells

Colloid and Adequacy

• Does the presence of colloid define an FNA as adequate?
    • Colloid without cells is “non-diagnostic”

  – The Thyroid Bethesda system
    • “Abundant colloid” lacking epithelial cells is benign
      – When is it abundant?
      – When is it colloid? - Problem with liquid based preparations
        » Loss of colloid through the filter
        » Less easily recognized
Colloid and Adequacy

**Personal Opinion**

- I do not accept abundant colloid lacking epithelial cells as benign –
  Unless no solid component on ultrasound
  - I know of no evidence to support this contention
    - It is in fact a rare situation
      - Usually you can find epithelial cells

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Lesional Heterogeneity

*All Thyroid Nodules are not Created Equal*

Fact Well-known to Surgical Pathologist
Lesional Heterogeneity

Cytology Preparations
Cytomorphology vs. Cytopreps

Cytomorphology vs. Cytopreps
Relevant Clinical Information

- **Demographics:** Age, sex
- **Nodule:** Single/multiple, size, growth, nature
- **History:** Head and neck irradiation
- **Family history:** Thyroid carcinoma
- **Non-palpable nodules:** >1.5cm/<1.5cm
- **Clinical features:** Hoarseness, dysphagia, dyspnea, regional lymphadenopathy
- **? Graves’ and Hashimoto’s disease**
Relevant Clinical Information Should be Provided to the Cytopathologist

- *Why? Thyroid mass or even better*  
  *Neck mass*
  
  - Thyroid function tests
  - Thyroid Scan
  - History of previous FNA

Clinical History is as Important as your diagnosis

*Thyroid FNA without history*

*Is this a test?*
Case 1

- 52-year-old woman
- Ultrasound – Left thyroid lobe occupied by a predominantly ill-defined hypoechoic structure – suspicious for anaplastic carcinoma
Cytologic Diagnoses

Case 1:
• Original Diagnosis Suspicious for Anaplastic Carcinoma
  – More History
    • Transient symptomatic hyperthyroidism (TSH – 0.03) followed by hypothyroidism.
    • Current medication: Synthroid
  – Second opinion Dx: Suspect sub-acute thyroiditis
  – Surgical excision of left lobe

Lesson Learned

• History is as important as your diagnosis
  – Nodule characteristics
  – TFT's
  – Prior FNA – Dx
Sampling

Fact well-known to surgical pathologist

Case of – Who Done It – The Sampling
**Case of – Who Done It – The Sampling**

Hemorrhagic 2.2 x 3.0 x 1.5 cm nodule
Adjacent 1.4 cm cystic nodule with papillary growth pattern.
Case of – Eager Patient or Clinician – Don’t tell the Pathologist of Prior FNA-3 days ago

Markedly Atypical Cells

Cytomorphology & Classification
Objectives of Thyroid FNA

- Recognize **specific** diagnostic entities
- Provide meaningful, management oriented **diagnosis**
- Potential utilization of ancillary techniques

**Thyroid FNA**

**Bethesda Classification Scheme**

*The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC): 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>Non-diagnostic 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>Atyopia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)</td>
<td>~ 5-15%</td>
<td>Repeat FNA</td>
</tr>
<tr>
<td>Follicular Neoplasm or Suspicious for a Follicular Neoplasm (Specify if Hurthle type or Oncocytic)</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>
The Timing of TBSRTC

Growing Body of Literature Showing Inconsistencies in Surgical Pathology Diagnosis of Thyroid Cancer Among Experts – Encapsulated Follicular Variant
The Cytology Gold Standard is not so Gold

Follow-up Clinicopathologic Studies Showing Over-diagnosis and Over-treatment of Thyroid Carcinoma – PTC.
Concept of Low and High Risk Disease

TBSRTC

Clinical and Radiology Guidelines
American & European Thyroid Association
American College of Radiology
American Society of Radiologist in Ultrasound

Molecular Profiling of Thyroid Tumors
Molecular Diagnosis of Thyroid Nodules
Diagnostic Tests with high Negative and Positive Predictive Value
Easy-Breezy of Thyroid Cytopathology

Concordant Ultrasound Features, FNA cytomorphology & Histologic Follow-up

Nodular Goiter

Colloid: Generally abundant. Follicular cells Variable morphology Oncocytes, Macrophages Degeneration/regeneration: Calcification, stromal proliferation, mitoses
Chronic Lymphocytic Thyroiditis

Oncocytes + Lymphocytes: In the background & infiltrating the cell groups

Papillary Thyroid Carcinoma

Nuclear features – Major Diagnostic Features
- Elongation, chromatin clearing
- Nuclear membrane irregularities
- Intranuclear grooves, Inclusions
- Small peripheral nucleoli
Not so easy - Head Scratching Everyday Thyroid Cytopathology

*Indeterminate Lesions*

*Or*

*Indeterminate Pathologist?*

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**Thyroid FNA**

**Bethesda Classification Scheme**

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</table>
Diagnosis Follicular Neoplasm

80% Benign on Surgical Excision

Diagnosis
Follicular Lesion / Neoplasm
“Microfollicles” in FNA Specimens

Microfollicles = Neoplasm

Microfollicles – We Don’t Agree

• Inter-observer Agreement on Microfollicles
  – Renshaw AA et al. (Arch Pathol Lab Med 2006)
  – 12 cytopathologists were shown 45 small groups of follicular cells
    • 20 Microfollicles
    • 7 Macrofollicles
    • 18 Indeterminate
  – <15 cells arranged in circle that is at least two-thirds complete, should be classified as microfollicles.
The Atypical Category

The Dreaded AUS/FLUS

Reasons for AUS/FLUS

• History
  – TFT’s, H/O prior FNA
• Ultrasound features
  – Cystic vs. solid
• Operator – sampling
• Adequacy
• Cytology Preparation
• Interpretation
• Surgical follow-up – ? Gold standard
How to Relay The AUS/FLUS Diagnosis

*Explain, Explain & Explain*

HUP Experience

- **AUS/FLUS cases are further sub-classified into Following subcategories (SC):**
  - SC1 - favor benign, however, a follicular neoplasm (FN) could not be excluded due to increased cellularity
  - SC2 - specimens with focal nuclear overlapping and crowding
  - SC3 - scant specimens with focal nuclear overlapping and crowding
  - SC4 - specimens with focal nuclear overlapping and crowding in a background of lymphocytic thyroiditis
  - SC5 - few cells with features suspicious for papillary thyroid cancer (PTC)
  - SC6 - specimens in which a FN cannot be excluded (with miscellaneous morphologic descriptors).

<table>
<thead>
<tr>
<th>Subclasses</th>
<th>Cases</th>
<th>Age ± SD</th>
<th>Size (mm) ± SD</th>
<th>Cases with Repeat FNA</th>
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<tbody>
<tr>
<td>SC1</td>
<td>13</td>
<td>41 ± 20</td>
<td>2.71 ± 1.20</td>
<td>7 (17.7%)</td>
</tr>
<tr>
<td>SC2</td>
<td>127</td>
<td>56 ± 17</td>
<td>2.55 ± 1.12</td>
<td>72 (56.5%)</td>
</tr>
<tr>
<td>SC3</td>
<td>128</td>
<td>59 ± 15</td>
<td>2.91 ± 1.05</td>
<td>64 (49.6%)</td>
</tr>
<tr>
<td>SC4</td>
<td>52</td>
<td>56 ± 15</td>
<td>2.14 ± 1.02</td>
<td>29 (55.8%)</td>
</tr>
<tr>
<td>SC5</td>
<td>17</td>
<td>51 ± 14</td>
<td>2.75 ± 1.18</td>
<td>11 (64.7%)</td>
</tr>
<tr>
<td>SC6</td>
<td>11</td>
<td>56 ± 17</td>
<td>2.74 ± 1.33</td>
<td>4 (36.4%)</td>
</tr>
</tbody>
</table>

*Preoperative diagnosis of thyroid nodules using the Bethesda System for Reporting Thyroid Cytopathology: a comprehensive review and meta-analysis.*

### Table

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Cases</th>
<th>Surgical Excision</th>
<th>Malignant</th>
<th>ROM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AUS/FLUS</strong></td>
<td>1906</td>
<td>805</td>
<td>194</td>
<td>24.10%</td>
</tr>
<tr>
<td><strong>FON/SFON/SHCN</strong></td>
<td>3182</td>
<td>2183</td>
<td>660</td>
<td>30.23%</td>
</tr>
</tbody>
</table>

Are We Overestimating the # of Malignant Cases by Calculating the Risk of Malignancy Based on Selected Group of Cases Undergoing Surgery?
Can we Calculate Overall Risk of Malignancy (OROM)?

<table>
<thead>
<tr>
<th></th>
<th>Total Cases</th>
<th>Surgical Excision</th>
<th>Malignant</th>
<th>ROM</th>
<th>OROM</th>
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<tr>
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<td>2183</td>
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<td>21%</td>
</tr>
</tbody>
</table>

Rate of Surgical Intervention?

<table>
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<th>Surgical Excision</th>
<th>Malignant</th>
<th>ROM</th>
</tr>
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<tbody>
<tr>
<td><strong>AUS/FLUS</strong></td>
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<td>805 (42%)</td>
<td>194</td>
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<tr>
<td><strong>FON/SFON/SHCN</strong></td>
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<td>660</td>
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**The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)**

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>ROM(%) 2007</th>
<th>ROM(%) 2007-2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic or Unsatisfactory</td>
<td>1-4</td>
<td>11-26</td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>0-3</td>
<td>4-9</td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance</td>
<td>7.5-11</td>
<td>19-38</td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular Neoplasm or Suspicious for a Follicular Neoplasm</td>
<td>15-30</td>
<td>26-40</td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>60-75</td>
<td>50-79</td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99</td>
<td>98-99</td>
</tr>
</tbody>
</table>

**Molecular Profiling of Thyroid Tumors + Molecular Diagnosis of Thyroid Nodules**

**Diagnostic Tests with High Negative and Positive Predictive Value**

- Mutational Analysis
- Gene Expression Classifier
- Next Gene Sequencing
Schematic representation of the Mitogen Activated Protein Kinase (MAPK) signalling pathway.


Papillary Thyroid Carcinoma
Mutations in Papillary Carcinoma

- **BRAF V600E**: 46-75%
- **RET/PTC**: 15%
- **RAS**: 15-43%
  - **PAX8-PPARγ**: 37%
  - **BRAF V601K**: ~75%

75% Papillary CA

Follicular Carcinoma
Mutations in Follicular Carcinoma

RAS (HRAS, KRAS & NRAS-Codons 12 & 61)

- Frequently NRAS-Codon 61 (67%)
- Seen in Follicular adenoma, follicular carcinoma and follicular variant of PTC
- Follicular adenoma (30%) & Follicular carcinoma (57%). Fukahori et al. Thyroid 22, 2012
- NRAS Codon 61 mutations are associated with distant metastases & RAS mutations are associated with poor overall survival
  - Fukahori et al. Thyroid 22, 2012
Gene Expression Classifier

Increase rate of Suspicious GEC - Afirma Results in Oncocytic Nodules

<table>
<thead>
<tr>
<th>Study</th>
<th>Suspicious nodules w/surgery</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrell et al. Endo Pract 2014</td>
<td>30</td>
<td>13 (43%)</td>
<td>17 (57%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 9 (69%) oncocytic lesions</td>
<td></td>
</tr>
<tr>
<td>Mohr et al. JCEM 2014</td>
<td>32</td>
<td>27 (84%)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 12 (44%) oncocytic lesions</td>
<td></td>
</tr>
<tr>
<td>Brauner et al. Thyroid 2015</td>
<td>43*</td>
<td>37 (84%)</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>Lastra et al. Cancer Cytopath 2014</td>
<td>48</td>
<td>26 (54%)</td>
<td>22 (46%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 15 (58%) oncocytic lesions</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>153</td>
<td>103 (67%)</td>
<td>50 (33%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 73 (71%) oncocytic lesions</td>
<td></td>
</tr>
</tbody>
</table>
Next-Generation Sequencing Assay
Nikiforov et al. *Cancer* 2014, 120:3627-34

Change in the Gold Standard of Thyroid Cytology
Changes in Surgical Pathology Diagnosis / Classification of “Low Risk Tumor(s)”

The Endocrine Society Working Group for Re-evaluation of the Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

Project Goals

- **Review** a cohort of cases by experts in the field of endocrine pathology
- **Establish** a consensus on diagnostic histologic criteria
- **Define** the risk of adverse events based on long follow-up
- **Recommend** new terminology that reflects tumor biology and patient outcome
**Naming**
Non-Invasive Follicular Variant of PTC
as anything but
“Not Carcinoma”

**New Terminology Recommendation**
“Non-invasive follicular thyroid neoplasm with papillary-like nuclear features“ (NIFTP)
*Adequate sampling of entire tumor capsule is required to establish this diagnosis*

- Molecular profile - RAS and RAS-like mutations
- Non-invasive FVPTC – Negligible risk of recurrence
- Invasive EFVPTC - Increased risk of distant metastases

---

**Integrated Genomic Characterization of Papillary Thyroid Carcinoma. Cell (2014)**

<table>
<thead>
<tr>
<th>MUTATIONS</th>
<th>Classic PTC</th>
<th>Encapsulated-FVPTC</th>
<th>Poorly Diff Thy CA</th>
<th>Anaplastic Thy CA</th>
<th>Follicular Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF V600E</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF K601E</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>NRAS</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>HRAS</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
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<td>++</td>
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<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSHR</td>
<td>+</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>GNAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>++</td>
</tr>
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**GENE FUSIONS**

| RET/PTC | +++ | | | | |
| PAX8/PPARG | ++ | +++ | | | |
| ALK fusions | + | ++ | + | |
| BRAF fusions | + | | | |
| ETV6/NTRK3 | + | | | |
| NTRK1 fusion | + | | | |

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*What’s in a Name?*
Follicular Adenoma
Non-Invasive

Follicular Carcinoma
Invasive (Tumor Capsule & Vascular Invasion)

Nuclear Features of PTC Absent

Nuclear Features of PTC Present

NIFTP
Well Demarcated
Solid and cystic
Usually mixed follicular growth pattern
Isolated papillae comprising <1% of tumor mass

FVPTC
Invasive (Tumor Capsule & Vascular Invasion)

Potential Issues with NIFTP Diagnosis

Ethical issues & Legal implications
– Should we reclassify cases diagnosed in the past as “Encapsulated FVPTC” to “NIFTP”?

NO
Standard of care – Past vs. Present
Potential Issues with NIFTP Diagnosis

Cytopathology Diagnosis Based on Nuclear Morphology

Increase in the number of False Positive diagnosis?

1. NIFTP is a Surgical Disease
2. Diagnosis based upon application of strict diagnostic criteria
**Noninvasive nature has to be documented based on adequate sampling of tumor periphery and capsule

Potential Issues with NIFTP Diagnosis

Cytopathology Diagnosis
Increase in the number of False Positive diagnosis?

Too early to tell
Most Encapsulated FVPTC are Classified as:
Follicular Neoplasm / Suspicious for Follicular Neoplasm
Or
Suspicious for Papillary Carcinoma
The Impact of NIFTP Diagnosis on Implied Risk of Malignancy of Diagnostic Categories of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)

<table>
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<th>FNA Diagnosis</th>
<th>Faquin et al.* Total Cases</th>
<th>% ROM</th>
<th>% ROM excluding NIFTP</th>
<th>% Decrease in ROM</th>
<th>Strickland et al. Total Cases</th>
<th>% ROM</th>
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<tr>
<td>ND</td>
<td>70</td>
<td>25.3</td>
<td>21.9</td>
<td>1.4</td>
<td>53</td>
<td>18.9</td>
<td>17.0</td>
<td>1.9</td>
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<tr>
<td>Benign</td>
<td>426</td>
<td>9.3</td>
<td>5.8</td>
<td>3.5</td>
<td>167</td>
<td>15.2</td>
<td>5.4</td>
<td>7.8</td>
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<tr>
<td>AUS/FLUS</td>
<td>397</td>
<td>31.2</td>
<td>17.6</td>
<td>13.6</td>
<td>97</td>
<td>39.2</td>
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<td>FN/SFN</td>
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<td>33.2</td>
<td>18.0</td>
<td>15.2</td>
<td>88</td>
<td>45.5</td>
<td>37.5</td>
<td>8.0</td>
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<td>SM</td>
<td>179</td>
<td>82.6</td>
<td>59.2</td>
<td>23.4</td>
<td>94</td>
<td>87.2</td>
<td>45.7</td>
<td>41.5</td>
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<tr>
<td>Malignant</td>
<td>450</td>
<td>99.1</td>
<td>95.7</td>
<td>3.4</td>
<td>156</td>
<td>98.7</td>
<td>93.6</td>
<td>5.1</td>
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</table>

*Multi-institutional study, ROM-risk of malignancy, NIFTP-non-invasive follicular tumor with papillary-like nuclei

New Terminology Recommendation
“Non-invasive follicular thyroid neoplasm with papillary-like nuclear features” (NIFTP)

*Adequate sampling of entire tumor capsule is required to establish this diagnosis

Changes in the Implied Risk of Malignancy for TBSRTC Categories

**AUS/FLUS**
Suspicious for Follicular Neoplasm
Suspicious for Malignancy – 50% decrease

(Strickland et al. Thyroid 2015 & Faquin et al. Cancer Cytopathology 2015)
## Table I

### Cytologic and Molecular Alterations in a Cohort of 39 NFVPTCs and cPTCs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ePTC, No. (%)</th>
<th>NFVPTC, No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspicious on FNA</td>
<td>6 (21)</td>
<td>11 (100)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Malignant on FNA</td>
<td>22 (79)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Microfollicle predominant</td>
<td>1 (4)</td>
<td>6 (65)</td>
<td>.0009</td>
</tr>
<tr>
<td>Sheet predominant</td>
<td>27 (96)</td>
<td>4 (36)</td>
<td>.0002</td>
</tr>
<tr>
<td>Papillae</td>
<td>14 (50)</td>
<td>0</td>
<td>.0030</td>
</tr>
<tr>
<td>Pseudoinclusions</td>
<td>22 (79)</td>
<td>0</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BRAF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14 (61)</td>
<td>0</td>
<td>.0018</td>
</tr>
</tbody>
</table>

ePTC, classical papillary thyroid carcinoma; FNA, fine-needle aspiration; NFVPTC, noninvasive follicular variant of papillary thyroid carcinoma.

<sup>a</sup> Molecular analysis was available for 23 cPTCs and nine NFVPTCs. One case of NFVPTC showed a mixed population of tumor sheets and microfollicles.


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## Cytologic and Histologic Correlation of FVPTC

Ashley A. Ibrahim MD, Howard H. Wu MD. AJCP Aug 20th, 2016

<table>
<thead>
<tr>
<th>Final Histologic Diagnosis on Thyroidectomy Specimens</th>
<th>Total No. of Cases</th>
<th>B, No. (%)</th>
<th>FLUS, No. (%)</th>
<th>FN, No. (%)</th>
<th>S/PTC, No. (%)</th>
<th>PTC, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrative FVPTC or encapsulated FVPTC with capsular and/or lymphovascular invasion</td>
<td>27</td>
<td>0 (0)</td>
<td>4 (15)</td>
<td>3 (11)</td>
<td>12 (44)</td>
<td>8 (30)</td>
</tr>
<tr>
<td>Encapsulated FVPTC, noninvasive</td>
<td>23</td>
<td>4 (17)</td>
<td>14 (61)</td>
<td>4 (17)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

<sup>b</sup> benign; FLUS, follicular lesion of undetermined significance; FN, follicular neoplasm; FVPTC, follicular variant of papillary thyroid carcinoma; PTC, papillary thyroid carcinoma; S/PTC, suspicious for papillary thyroid carcinoma.
Maletta, F. et al. Cytological features of "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" and their correlation with tumor histology. *Hum Pathol* 2016

<table>
<thead>
<tr>
<th></th>
<th>NIFTP</th>
<th>Benign follicular lesions</th>
<th>Invasive EFVPTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>96</td>
<td>37</td>
<td>24</td>
</tr>
<tr>
<td>Age (yrs, median)</td>
<td>46</td>
<td>62</td>
<td>43</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>70</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Male</td>
<td>26</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Size (cm, mean)</td>
<td>2.6</td>
<td>3.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Cytological categories according to the Bethesda System

<table>
<thead>
<tr>
<th>Category</th>
<th>NIFTP</th>
<th>Benign follicular lesions</th>
<th>Invasive EFVPTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>II⁰</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III (%)⁰</td>
<td>14 (15)</td>
<td>17 (46)</td>
<td>0</td>
</tr>
<tr>
<td>IV (%)⁰</td>
<td>54 (56)</td>
<td>20 (54)</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>V (%)⁰</td>
<td>26 (27)</td>
<td>0</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>VI (%)⁰</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The Future of Thyroid FNA in NIFTP Paradigm

Still Need More Data to Provide Opinions
Conclusions?

• NIFTP
  – Beneficial to patients
  – Stricter set of exclusion criteria
  – Grossing of encapsulated or well demarcated nodule
  – Initial pathologic approach to diagnose and manage low-risk thyroid neoplasms.

What to expect – too early to tell
NIFTP is a surgical disease

• Change in the malignancy risk for Bethesda Classification categories especially “suspicious for PTC” 50-60%.
• Should the suspicious category be divided? Suspicious for malignancy & PTC?
• Change in the malignancy risk for AUS/FLUS & Follicular Neoplasm / Suspicious for Follicular Neoplasm
**What criteria I should use to diagnose “consistent with PTC”?**

- Before Opinions?
  - Consider sampling issues, ultrasound features and disease presentation
  - True papillae – presence of fibrovascular core(s)?
  - Diffuse rather than focal presence of “major diagnostic nuclear features of PTC”

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**If rendering a diagnosis of “Suspicious for PTC”**

- Suspicious for papillary thyroid carcinoma, see note.
  - Note: The specimen shows a distinct population of atypical follicular cells with nuclear features suspicious but not diagnostic of papillary thyroid carcinoma. According to the published data 50-75% of thyroid FNA cases diagnosed as such are found to be malignant on surgical excision. The histologic follow-up of thyroid FNA cases diagnosed as such can include one of the following entities: papillary thyroid carcinoma and non-invasive follicular tumor with papillary like nuclei (NIFTP).
- Molecular Analysis
  - Which test – Mutation and Translocation Panel
**Possible Recommendations for Thyroid FNA Specimens**


<table>
<thead>
<tr>
<th>TRISS Category</th>
<th>Sign-Out Modification</th>
<th>Explanatory Note for Potential NIFTP Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADI</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>Identify a subset of follicular-patterned lesions with mild nuclear changes (nuclear enlargement, chromatin clearing, and/or nuclear contour irregularities)</td>
<td>Note: Although the architectural features suggest a follicular neoplasm, some nuclear features raise the possibility of a follicular variant of papillary carcinoma or an erratically arranged follicular variant. NIFTP: definitive distinction among these entities is not possible on cytologic material.</td>
</tr>
<tr>
<td>NAI</td>
<td>Identify a subset of cases suspicious for PTC that have microfollicular architecture and lack intranuclear pseudoinclusions, papillae, or psammoma bodies</td>
<td>Note: The overall cytomorphologic features are suggestive of a papillary variant of follicular carcinoma or a follicular variant of papillary carcinoma. NIFTP: definitive distinction between these entities is not possible on cytologic material.</td>
</tr>
<tr>
<td>Malignant</td>
<td>Limit to cases with frequent pseudoinclusions, papillae, or psammoma bodies along with other cytologic features of PTC (explanatory note is optional)</td>
<td>Note: With the reclassification of some indolent thyroid tumors as NIFTP, the positive predictive value of the malignant category for thyroid FNA is expected to drop from 99% to about 94%-96%; thus, a small proportion of cases currently assigned to this category may prove to be NIFTP on histologic examination.</td>
</tr>
</tbody>
</table>

Abbreviations: AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FNA, fine-needle aspiration; ND, nondiagnostic; PTC, papillary thyroid carcinoma; SUS, suspicious; SFN/FN, suspicious for a follicular neoplasm/follicular neoplasm; TBSRTC, The Bethesda System for Reporting Thyroid Cytopathology.

**Thyroid nodules are Common**

2012 450,000 FNAs estimated in USA

![Graph showing prevalence of thyroid nodules by age](image)

- Palpation
- Autopsy & US

• **The Data from future thyroid FNA studies based on changes in surgical pathology diagnoses** will be important for recommending potential changes in TBSRTC

• **The Adjunct Molecular tests are here to stay**
  - Never going to replace thyroid FNA cytology
  - Play a role in the current management paradigm of thyroid nodules