Cytomorphologic Thresholds for Classifying Thyroid FNAs as “Suspicious” and “Positive” for PTC

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Dr. Tarik Elsheikh declares he has no conflict(s) of interest to disclose.

• 2.5 cm R thyroid nodule in a 36 YO woman

Case Study

How should we sign this case out?
A. AUS/FLUS
B. FN/SFN
C. Susp. for PTC
D. Positive for PTC

Surgical Follow-up:
- Infiltrative FVPTC with ETE

Major Challenges and Controversies in Diagnoses of “Suspicious” and “Positive” for PTC

• Positive for PTC
  - Minimal criteria for a definitive DX of PTC
• Suspicious for PTC
  - How much atypia is enough?
  - Where do you draw the line between “Suspicious for PTC” and “AUS/FLUS”?
• NIFTP
  - Impact on cytologic Dx and ROM
  - Management implications

TBSRTC and Management Recommendations

<table>
<thead>
<tr>
<th>Categories</th>
<th>ROM</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diagnostic</td>
<td>&lt;3%</td>
<td>Repeat FNA (US)</td>
</tr>
<tr>
<td>Benign</td>
<td></td>
<td>Clinical, US F/U</td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>5-15%</td>
<td>F/U, repeat FNA, molecular</td>
</tr>
<tr>
<td>FN/SFN</td>
<td>20-30%</td>
<td>Lobectomy</td>
</tr>
<tr>
<td>SM</td>
<td>50-75%</td>
<td>Lobectomy ± FS or TT</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99%</td>
<td>Total thyroidectomy</td>
</tr>
</tbody>
</table>

• Surgical management of SM should be similar to malignant cytology (2015 ATA guidelines: strong recommendation)
Classic PTC

- Branching monolayered sheets: most significant low power discriminator from Follicular neoplasm (Fulwala 2001)

Follicular Variant of PTC

- 2nd most common variant of PTC, approx. 30% of cases
- Second to sampling error as most common cause of false negative DXs

FVPTC

- Squamoid cytoplasm
- Oval enlarged nuclei, powdery chromatin
- Grooves/irregular nuclear membranes
- Margined nucleoli
- Intranuclear holes

Suspicious for PTC

- Strong suspicion for malignancy

**Cytologic criteria:**

1. **Quantitative:**
   - PTC features well developed but either focal/patchy or very sparse cellularity

2. **Qualitative:**
   - Diffuse but incomplete nuclear changes of PTC
     - i.e. generalized nuclear enlargement and pallor, but rare grooves or inclusions
     - Hypervacuolated and atypical histiocytoid cells

- FVPTC may show:
  - Paucity of nuclear features of PTC
  - Abundant colloid
  - Misdiagnosed as B9 or AUS/FLUS
Suspicious for PTC

Sensitive cytologic criteria for detecting FVPTC

- Flat syncytial sheets
- Nuclear enlargement
- Fine chromatin
- Nuclear grooves
- <½ FVPTC showed intra-nuclear holes

Most sensitive
Most specific

(Wu 2003)

COMBINED

in

same

nuclei

ROM 75%

Suspicious for PTC

- Nuclear enlargement
- Powdery chromatin
- Focal grooves

AUS/FLUS

- Rare cells with distinct mild focal nuclear atypia
- More commonly associated with LT and cyst, occasionally with FVPTC

Atypical Histiocytoid cells in PTC

"An Under-recognized cytologic pattern"

- Resemble histiocytes but larger
- Enlarged nuclei, abundant vacuolated cytoplasm
- No grooves, no prominent inclusions
- Cystic PTC may be dominated by these macrophage-looking cells
- Potential pitfall → false negative Dx
- AE1/3+, TTF1+, CD68-

(Canepa 2017)
Susp for PTC
- Common pitfall: atypia associated with LT misdiagnosed as “PTC”
- Threshold for atypia should be increased in LT

NIFTP
- “Non-invasive follicular thyroid neoplasm with papillary-like nuclear features”
- New terminology recommended by EPS to replace “non-invasive encapsulated FVPTC”
- Approx 18% of PTC
- Extremely indolent biology, not warranting designation of cancer (< 1% recurrence/mets)
- NIFTP is a surgical disease
- Goal is to decrease overtreatment → lobectomy only with no adjuvant RAI

Effect of NIFTP on ROM
- Reclassifying NI-FVPTC would significantly decrease ROM of indeterminate DXs, especially “SM”
- No significant impact on ROM of benign and malignant Dx’s

How Will NIFTP Terminology Impact Our Cytology Practice?
1. Should we refine cytologic criteria of indeterminate DXs so that ROM remains unchanged?
2. Adopt a less aggressive management approach to coincide with decreased ROM for each TBSRTC category?
3. Influence choice of molecular testing?
1. Should we revise cytologic criteria of indeterminate DXs so that ROM remains unchanged?

i.e. downgrade “Malignant” → SM, or SM → FN/SFN or AUS/FLUS

- **Classic PTC vs. NIFTP (NI-FVPTC)**
  - Classic PTC: papillary structures, nuclear inclusions, psammoma bodies
  - NIFTP: microfollicular pattern

- **Invasive FVPTC vs NIFTP (NI-FVPTC)**
  - Cytology can not distinguish between them
  - NIFTP has more subtle features, whereas inv. FVPTC has more diffuse atypia
  - Majority of NIFTP (55-78%) are already being diagnosed as AUS/FLUS and FN/SFN
  - Great majority of inv. FVPTC (71-74%) are diagnosed as SM and positive for PTC - Bizzarro 2016, Ibrahim 2016

Anticipated ROM Changes Associated with TBSRTC Categories

<table>
<thead>
<tr>
<th>Diagnostic Categories</th>
<th>Pre-NIFTP</th>
<th>Post-NIFTP</th>
<th>Cytologic Criteria?</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUS/FLUS</td>
<td>10-30</td>
<td>10-30</td>
<td>No</td>
<td>F/U, repeat FNA, molecular testing</td>
</tr>
<tr>
<td>FN/SFN</td>
<td>25-40</td>
<td>10-40</td>
<td>No</td>
<td>Lobectomy, molecular</td>
</tr>
<tr>
<td>SM</td>
<td>50-75</td>
<td>45-60</td>
<td>No</td>
<td>Lobectomy, TT</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99</td>
<td>94-96</td>
<td>No</td>
<td>TT</td>
</tr>
</tbody>
</table>

- B9 and malignant: No significant change in ROM
- FN/SFN: Slight decrease in ROM, but not rate of neoplasia

1. Should we revise cytologic criteria of indeterminate DXs so that ROM remains unchanged?²

**Invasive FVPTC vs NIFTP (NI-FVPTC)**
- Cytology can not distinguish between them
- NIFTP has more subtle features, whereas inv. FVPTC has more diffuse atypia
- Majority of NIFTP (55-78%) are already being diagnosed as AUS/FLUS and FN/SFN
- Great majority of inv. FVPTC (71-74%) are diagnosed as SM and positive for PTC - Bizzarro 2016, Ibrahim 2016

2. Adopt a less aggressive management approach to coincide with decreased ROM?

- i.e. lobectomy (not TT) for SM?

2015 ATA Management Guidelines for Indeterminate Cytology DX’s
- Extent of surgery for indeterminate thyroid nodules is based on estimated pre-surgical malignancy risk & other US and clinical factors (ATA strong recommendation):
  - Nodule size
  - Family history
  - Radiation history
  - Patient preference
  - Contralateral nodularity
  - Medical comorbidities
  - Cytologic category
  - Hyperthyroidism

3. Influence choice of molecular testing?

- **Pre-NIFTP:**
  - Not recommended to determine extent of surgery
  - Not recommended for SM or malignant

- **Post-NIFTP:**
  - High PPV test (ThyroSeq v2 or ThyGenX) for SM
  - Help determine extent of surgery: lobectomy vs. TT
Summary & Personal Recommendations

Positive for PTC (malignant):
- Do not revise cytologic criteria of "positive for PTC"
- ROM is minimally affected by NIFTP (2-3% decrease)
- No anticipated change in management: TT
- Cytology can not distinguish between invasive FVPTC and NIFTP
- Explanatory note to include NIFTP in DDx is appropriate

Summary & Personal Recommendations²

Suspicious for PTC:
- ROM for "SM" is most impacted by NIFTP terminology
  - But remains considerably high at 45-60%
- Would not consider revising cytologic criteria
- Should communicate with clinicians regarding revising management approach, i.e. lobectomy vs. TT
  - Cytology alone does not determine extent of surgery
- Explanatory note to include NIFTP in DDx- optional, but not necessary

Suspicious for PTC
- Diffuse combined nuclear enlargement and powdery chromatin + significant # of grooves (not a majority of cells but found with ease)

- Subtle PTC features (nuclear enlargement + fine chromatin + rare grooves or an inclusion → Diagnose as FN/SFN or AUS/FLUS (depending on cellularity and architecture)

THANK YOU