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

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Case Study
2.5 cm R thyroid nodule in a 36 YO woman
How should we sign this case out?
A. AUS/FLUS  
B. FN/SFN  
C. Susp. for PTC  
D. Positive for PTC

Surgical Followup:
• 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 and positive for PTC?
  - 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></td>
<td>Repeat FNA (US)</td>
</tr>
<tr>
<td>Benign</td>
<td>&lt;3%</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 *(ATA strong recommendation)*
Classic PTC
Follicular Variant of PTC

- Second to sampling error as most common cause of false negative DXs

(Wu 2006)
Branching monolayered sheets: most significant low power discriminator from FN/SFN  
(Fulciniti 2001)
• Squamoid cytoplasm
• Oval enlarged nuclei, powdery chromatin
• Grooves/irregular nuclear membranes
• Marginated nucleoli
• Intranuclear holes
• **FVPC may show:**
  – Paucity of nuclear features of PTC
  – Abundant colloid
  – Misdiagnosed as B9 or AUS/FLUS
Suspicious for PTC

– Strong suspicion for malignancy

Cytologic criteria:

1. Quantitative:
   • PTC features present but very sparse cellularity
   • Patchy/focal nuclear changes of PTC

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
Suspicious for PTC

• Sensitive cytologic criteria for detecting FVPC
  – Flat syncytial sheets
  – Nuclear enlargement
  – Fine chromatin
  – Nuclear grooves

• <½ FVPC showed intra-nuclear holes

• Important NOT to lump these cases with other lower risk “indeterminate” Dx’s of “AUS/FLUS” and “FN/SFN”
Suspicious for PTC

- Nuclear enlargement
- Powdery chromatin
- Focal grooves

**COMBINED in same nuclei**

**ROM 75%**
• Generalized nuclear enlargement, powdery chromatin, occasional grooves
• Rare cells with distinct mild focal nuclear atypia
• More commonly associated with LT and cyst
• Occasionally with FVPC
• Hypervacuolated and atypical histiocytoid cells
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-
Susp for PTC

- **Common pitfall:** atypia associated with CLT misdiagnosed as “PTC”
- Threshold for atypia should be increased in lymphocytic thyroiditis
• PTC associated with LT
NIFTP

• "Non-invasive follicular thyroid neoplasm with papillary-like nuclear features”
• New terminology recommended by EPS to replace “non-invasive encapsulated FVPTC”
• Approx 15-20% of PTC
• Extremely indolent biology, not warranting designation of cancer (< 1% recurrence/mets)
• Goal is to decrease overtreatment → lobectomy only with no adjuvant RAI
# NIFTP and TBSRC Diagnoses

## Distribution of FNA DXs in NIFTP Cases

<table>
<thead>
<tr>
<th></th>
<th># Cases</th>
<th>Benign</th>
<th>AUS/FLUS</th>
<th>SFN</th>
<th>SM</th>
<th>PTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howitt 2015</td>
<td>72</td>
<td>12.5 %</td>
<td>18 %</td>
<td>9.7 %</td>
<td>48.6 %</td>
<td>7 %</td>
</tr>
<tr>
<td>Maletta 2016</td>
<td>96</td>
<td>0 %</td>
<td>15 %</td>
<td>56 %</td>
<td>27 %</td>
<td>2 %</td>
</tr>
<tr>
<td>Ibrahim 2016</td>
<td>23</td>
<td>17 %</td>
<td>61 %</td>
<td>17 %</td>
<td>4 %</td>
<td>0</td>
</tr>
<tr>
<td>Faquin 2016 (5 institutions)</td>
<td>173</td>
<td>9 %</td>
<td>31 %</td>
<td>27 %</td>
<td>24 %</td>
<td>9 %</td>
</tr>
</tbody>
</table>

- Reclassifying NI-FVPTC has most impact on indeterminate categories: \(~80\% ~of~ \textit{NIFTP} ~would~ be~ diagnosed~ as~ ”indeterminate”\)
- Variable thresholds for diagnosing SM
Effect of NIFTP on TBSRTC and ROM

- Reclassifying NI-FVPTC as “B9” would significantly decrease ROM of indeterminate DXs, especially “SM”
- No significant impact on ROM of benign and malignant Dx’s

<table>
<thead>
<tr>
<th></th>
<th>Pre-NIFTP ROM %</th>
<th>Post-NIFTP ROM %</th>
<th>% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>9.3</td>
<td>5.8</td>
<td>3.5</td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>31.2</td>
<td>17.6</td>
<td>13.6</td>
</tr>
<tr>
<td>SFN</td>
<td>33.2</td>
<td>18</td>
<td>15.1</td>
</tr>
<tr>
<td><strong>SM</strong></td>
<td><strong>82.6</strong></td>
<td><strong>59.2</strong></td>
<td><strong>23.4</strong></td>
</tr>
<tr>
<td>Malignant</td>
<td>99.1</td>
<td>95.7</td>
<td>3.3</td>
</tr>
</tbody>
</table>

*Faquin 2016*
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. Influences choice of molecular testing?
1. Should we refine cytologic criteria of indeterminate DXs so that ROM remains unchanged?

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

• Invasive FVPTC vs non-invasive FVPTC (NIFTP)
  – Cytology can not distinguish between them
  – NIFTP had more subtle features, whereas FVPTC had more diffuse atypia

• Classic PTC vs. NIFTP
  – Classic PTC: papillary structures, nuclear inclusions, psammoma bodies
  – NIFTP: microfollicular pattern
  – No differences in rates of nuclear grooves and irregularities- Glass 2016

### Anticipated ROM Changes Associated with TBSRTC Categories

<table>
<thead>
<tr>
<th>Diagnostic Categories</th>
<th>Risk of Malignancy %</th>
<th>Revise Cytologic Criteria?</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-NIFTP</td>
<td>Post-NIFTP</td>
<td></td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>10-30</td>
<td>10-30</td>
<td>No</td>
</tr>
<tr>
<td>FN/SFN</td>
<td>25-40</td>
<td>10-40</td>
<td>No</td>
</tr>
<tr>
<td>SM</td>
<td>50-75</td>
<td>45-60</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99</td>
<td>94-96</td>
<td>No</td>
</tr>
</tbody>
</table>

- Consider revising/increasing threshold of atypia for “SM” diagnoses, bec of potential impact on extent of surgery
1. Should we refine cytologic criteria of indeterminate DXs so that ROM remains unchanged? ²

- Explanatory note in report?
  - Include NIFTP in DDx of SM and malignant diagnoses: “a small proportion of cases may prove to be NIFTP on histological examination”
2. Adopt a more aggressive management approach to coincide with revised/decreased ROM for each TBSRTC category?

- i.e. Lobectomy (not TT) for SM or
- Molecular testing (not lobectomy) for FN (*Lobectomy is current SOC*)

**2015 ATA Management Guidelines for SM and 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
Summary & Personal Recommendations

- 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 optional
- Combined presence of nuclear enlargement, fine chromatin, and grooves in majority of cells is diagnostic of PTC
- Papillae and/or nuclear pseudo-inclusions are helpful, but not required for a definitive diagnosis of PTC
Summary & Personal Recommendations

- ROM for “Susp. for PTC” is most impacted post-NIFTP
  - Lower ROM may result in unnecessary TT
- Should consider revising cytologic criteria, especially if threshold for atypia was low pre-NIFTP
- Explanatory note to include NIFTP in DDx- optional
Diffuse nuclear enlargement and powdery chromatin, in addition to significant # of grooves (found with ease)

Suspicious for PTC
• Cases with more subtle PTC features (nuclear enlargement + fine chromatin + rare grooves or inclusions \rightarrow Downgrade to FN/SFN or AUS/FLUS (depending on cellularity)
Thank You!