Overview of Indeterminate Cytology

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DISCLOSURE

Nothing to disclose
Learning Objectives

- Understand the origins of indeterminate cytology results
- Appreciate the differences among the indeterminate cytology categories
- Investigate the use of non-molecular techniques in resolving indeterminate results
- Explore the limitations of non-molecular techniques in resolving indeterminate results
Atypia of undetermined significance (AUS) / follicular lesion of undetermined significance (FLUS)

Follicular neoplasm

Suspicious for carcinoma
The Problem

AUS / FLUS

- 2 to 27% of thyroid FNA diagnoses
  - Marked variability in use, often too frequent
    - "Target rate" of AUS diagnoses:
      - 7% of diagnoses
      - AUS / malignant ratio between 1.0 to 3.0
  - “Risk of malignancy”:
    - 5 to 15% (NCI) / 3 to 50% (literature)

- Clinical dilemma
  - What do you do now?
The Problem

- Follicular (or Hürthle cell) neoplasm
  - Synonyms
    - Suspicious for follicular (or Hürthle cell) neoplasm
  - 1 to 25% of thyroid FNA diagnoses (usually ~10%)
  - “Risk of malignancy”
    - 15 to 30% (NCI) / 8 to 85% (literature)
  - Clinical dilemma
    - Lobectomy vs. total thyroidectomy?
Appellation Misapprehension

Follicular neoplasm ≠ Follicular lesion
The Problem

- Suspicious for carcinoma
  - 2 to 6% of thyroid FNA diagnoses
  - Majority are suspicious for PTC
  - “Risk of malignancy”
    - 60 to 75% (NCI) / 21 to 100% (literature)
  - Clinical dilemma
    - Lobectomy vs. total thyroidectomy?
Origins of Indeterminates

Sample related
- Inadequate lesional sampling
- Cytopreparation issues

Lesional characteristics
- FVPTC

Interpretative

Definitional
- Capsular / vascular invasion defines malignancy
Resolving The Indeterminates

An once of prevention
  – Better sampling and cytoprep

Clinical
  – Patient characteristics
  – Lesional characteristics
    – Imagining - ultrasound characteristics / PET
  – “Reading between the lines”
Reading Between The Lines

The report’s description is a cryptogram that can be deciphered to learn the “truth”

- Based on the fallacy that pathologists are perfect / objective observers
  - What has been “seen”, may not be true
    - A misinterpretation
  - What was not “seen” may be diagnostically critical
- Perhaps an indicator to have the case reviewed
Resolving The Indeterminates

Repeat sampling
– Thematic variation
  Alternative sampling devices (large bore needle)
– Repeat sampling may address:
  Inadequate lesional sampling
  Cytopreparation issues
  Interpretative issues
– Primarily for AUS/FLUS & Suspicious
  ☑ Cannot address definitional issues
    ▶ Minimal utility in follicular neoplasms
Repetitive Sampling

- Outcomes of repeat FNA
  - Poorly studied
    - Retrospective, based on diagnostic reassignment, admixture of indeterminate categories, small numbers, selection bias, more than 1 repeat FNA, incomplete follow-up for repeat FNA, incomplete outcome follow-up
      - Usually <40% indeterminate patients get repeat FNA
      - Smaller number with surgical follow-up
Repetitive Sampling

Outcomes of repeat FNA

- Resolution - definitive FNA diagnosis: 42-65%

Limitations

- Resource intensive
- Additional harm done (patient & lesion)
- Many remain unresolved: 35-68%
  - Repeat FNA non-diagnostic: 1-31%
# AUS Repetitive Sampling

<table>
<thead>
<tr>
<th>n = 516¹-³</th>
<th>Histology</th>
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<tbody>
<tr>
<td>Repeat FNA</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>142</td>
</tr>
<tr>
<td>Benign</td>
<td>185</td>
</tr>
<tr>
<td>Benign</td>
<td>2</td>
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<tr>
<td>Benign</td>
<td>187</td>
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<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>98.6%</td>
</tr>
<tr>
<td>Specificity</td>
<td>50.3%</td>
</tr>
<tr>
<td>PPV</td>
<td>43.4%</td>
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<tr>
<td>NPV</td>
<td>98.9%</td>
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<tr>
<td>FP Rate</td>
<td>49.7%</td>
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<tr>
<td>FN Rate</td>
<td>1.4%</td>
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4,924 AUS FNA¹-³
1,856 (37.7% repeat FNA)
523 (10.6% biopsy follow-up)

PPV of AUS FNA 15.9%⁴
NPV of Benign FNA 96.3%⁴

Resolving The Indeterminates

Pathologically

- Second cytology reviews
  - Consensus reviews

- Morphologic / morphometric parameters

- Immunohistochemistry

- Genetic alterations
Second Cytology Reviews

Addresses only interpretative issues
– No impact on
  - Sampling inadequacies
  - Cytopreparatory deficiencies
  - Lesional issues
  - Definitional issues

Outcomes of second cytology reviews

- Poorly studied
  ▶ Retrospective, diagnostic reassignment, admixture of indeterminate categories, small numbers, selection bias, unblinded, incomplete follow-up
Second Cytology Reviews

Outcomes of second cytology reviews

- Resolution - definitive FNA diagnosis
  - AUS: 41-43%
  - FN: 24-51%
  - Suspicious for malignancy: 38-68%

Limitations

- Resource consumption - low
- Many remain unresolved: 32-76%
  - Review Result: non-diagnostic: 2-15%
AUS - Second Reviews

n = 132

<table>
<thead>
<tr>
<th>Second Review</th>
<th>Malignant</th>
<th>Benign</th>
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<tbody>
<tr>
<td>Abnormal</td>
<td>60</td>
<td>35</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>36</td>
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</table>

Sensitivity 98.4%
Specificity 50.7%
PPV 63.2%
NPV 97.3%
FP Rate 49.3%
FN Rate 1.6%

Repeat FNA
43.4%
98.9%

PPV of AUS FNA 15.9%
NPV of Benign FNA 96.3%

825 AUS FNA second review
140 (17.0% biopsy follow-up)

2. Endocr J. 2012;59(3):205-12
# FN - Second Reviews

<table>
<thead>
<tr>
<th>n = 116&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Surgery</th>
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<tr>
<td><strong>Second Review</strong></td>
<td><strong>Malignant</strong></td>
<td><strong>Benign</strong></td>
</tr>
<tr>
<td>Abnormal</td>
<td>22</td>
<td>84</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>9</td>
</tr>
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</table>


443 FN FNA second review
121 (27.3% biopsy follow-up)

Sensitivity 95.7%
Specificity 9.7%
PPV 20.8%
NPV 90.0%
FP Rate 90.3%
FN Rate 4.3%

NPV of Benign FNA 96.3%<sup>2</sup>
PPV of FN FNA 26.1%<sup>2</sup>
### Suspicious - Second Reviews

<table>
<thead>
<tr>
<th>n = 379(^{1-2})</th>
<th>Surgery</th>
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</thead>
<tbody>
<tr>
<td><strong>Second Review</strong></td>
<td><strong>Malignant</strong></td>
</tr>
<tr>
<td><strong>Abnormal</strong></td>
<td>349</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>2</td>
</tr>
</tbody>
</table>

| Sensitivity | 99.4% |
| Specificity | 17.9% |
| PPV         | 93.8% |
| NPV         | 71.4% |
| FP Rate     | 82.1% |
| FN Rate     | 0.6%  |

562 Susp FNA second review
396 (70.5% biopsy follow-up)

PPV of Susp FNA 75.2\(^3\)
NPV of Benign FNA 96.3\(^3\)

2. Endocr J. 2012;59(3):205-12
Repeat or Re-Review

Second review is possibly better than repeat FNA?

- Data validity questionable
- Primarily for AUS and Suspicious categories
  - No assistance for follicular neoplasm?

- Second review advantages
  - Less cost
  - Less harm

- Second review limitation
  - Garbage in garbage out
Immunohistochemistry

Premise
- Aberrant antigen expression identifies malignancy
  - No absolute marker of malignancy

Requires reasonably abundant tissue
- Handicapped by sampling issues

Optimization and validation of staining a challenge
Immunohistochemistry

Numerous antigens investigated:

– Cytokeratin 19 (CK19)
– HBME-1
– Galectin-3
– Others
  ❖ Cyclin D1/D3
  ❖ CD57
  ❖ GLUT-1
  ❖ Fibronectin-1
  ❖ More
Immunohistochemistry

- Has not gained widespread application
  - Inconsistency of results
    - Variability in pretesting sample preparation (fixation)
    - Lack of standardization of testing
      - Antibody clones, dilutions, pre-treatments, etc.
    - Interpretative difficulties
    - Overlap in expression with benign entities
Ideal Universe
Managing the Indeterminates

- High quality FNA sample
- Refined “expert” cytologic diagnoses
- Non-molecular techniques to resolve the indeterminates are poorly studied
  - Appear of limited utility