83rd Annual Meeting

American Thyroid Association

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

The Indeterminates

- 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

n = 516[1-3]	Histology	
Repeat FNA	***Malignant***	***Benign***
Abnormal	**142**	**185**
Benign	**2**	**187**

4,924 AUS FNA[1-3]
1,856 (37.7% repeat FNA)
523 (10.6% biopsy follow-up)

Sensitivity	98.6%
Specificty	50.3%
PPV	43.4%
NPV	98.9%
FP Rate	49.7%
FN Rate	1.4%

PPV of AUS FNA 15.9%[4]

NPV of Benign FNA 96.3%[4]

1. Diagn Cytopathol. 2010;38(10):731-9
2. Am J Clin Pathol. 2011;135(5):770-5
3. *Acta Cytol*. 2012;56(4):361-9
4. *Acta Cytol*. 2012;56(4):333-9

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[1-2]	Surgery	
Second Review	***Malignant***	***Benign***
Abnormal	**60**	**35**
Negative	**1**	**36**

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

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

PPV of AUS FNA 15.9%[3]

NPV of Benign FNA 96.3%[3]

Repeat FNA
43.4%
98.9%

1. J Clin Endocrinol Metab. 2013;98(4):1450-7
2. Endocr J. 2012;59(3):205-12
3. *Acta Cytol*. 2012;56(4):333-9

FN - Second Reviews

n = 116[1]	Surgery	
Second Review	***Malignant***	***Benign***
Abnormal	**22**	**84**
Negative	**1**	**9**

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

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

PPV of FN FNA 26.1%[2]

NPV of Benign FNA 96.3%[2]

1. J Clin Endocrinol Metab. 2013;98(4):1450-7
2. Acta Cytol. 2012;56(4):333-9

Suspicious - Second Reviews

n = 379[1-2]	Surgery	
Second Review	***Malignant***	***Benign***
Abnormal	**349**	**23**
Negative	**2**	**5**

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

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

PPV of Susp FNA 75.2%[3]

NPV of Benign FNA 96.3%[3]

1. J Clin Endocrinol Metab. 2013;98(4):1450-7
2. Endocr J. 2012;59(3):205-12
3. *Acta Cytol*. 2012;56(4):333-9

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