Thyroid Nodule Evaluation & Office Based Ultrasound-FNA

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Agenda

- Thyroid Nodule Evaluation
  - Current Guidelines
  - Indeterminate Cytology & Molecular Markers
  - Role of Pre-operative Ultrasound
- Using Ultrasound in the Office
  - Diagnostic Neck Ultrasound
  - US-FNA Procedures
  - Coding
Thyroid Ultrasound

R2 Thyroid sonography should be performed in all patients with known or suspected thyroid nodules (A)

ATA guidelines, Cooper DS, Thyroid, 2009

- Is the palpable abnormality a thyroid nodule?
- Are other nodules present?
- Size?
- Suspicious features?
- > 50% cystic?
- Posterior?
- Associated abnormal lymph nodes?

ATA 2009

<table>
<thead>
<tr>
<th>Nodule Sonographic / Clinical Features</th>
<th>Recommended nodule threshold size for FNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk history*</td>
<td>≥5 mm</td>
</tr>
<tr>
<td>Node WITH suspicious sonographic features**</td>
<td>Recommendation A</td>
</tr>
<tr>
<td>Node WITHOUT suspicious sonographic features**</td>
<td>≥5 mm</td>
</tr>
<tr>
<td>Recommendation I</td>
<td></td>
</tr>
<tr>
<td>Abnormal cervical lymph nodes</td>
<td>All**</td>
</tr>
<tr>
<td>Recommendation A</td>
<td></td>
</tr>
<tr>
<td>Microcalcifications present in Nodule</td>
<td>≥1cm</td>
</tr>
<tr>
<td>Recommendation B</td>
<td></td>
</tr>
<tr>
<td>Solid nodule</td>
<td>≥1cm</td>
</tr>
<tr>
<td>AND hypoecholic</td>
<td>Recommendation B</td>
</tr>
<tr>
<td>AND iso- or hyperecholic</td>
<td>≥1-1.5cm</td>
</tr>
<tr>
<td>Recommendation C</td>
<td></td>
</tr>
<tr>
<td>Mixed cystic/solid nodule</td>
<td>≥1.5-2.0cm</td>
</tr>
<tr>
<td>WITH any suspicious ultrasound feature**</td>
<td>Recommendation B</td>
</tr>
<tr>
<td>WITHOUT suspicious ultrasound features</td>
<td>≥2cm</td>
</tr>
<tr>
<td>Recommendation C</td>
<td></td>
</tr>
<tr>
<td>Spongiform nodule</td>
<td>≥2cm***</td>
</tr>
<tr>
<td>Recommendation C</td>
<td></td>
</tr>
<tr>
<td>Purely cystic nodule</td>
<td>FNA not indicated****</td>
</tr>
<tr>
<td></td>
<td>Recommendation E</td>
</tr>
</tbody>
</table>
What Constitutes a High Risk History?

Prior radiation (in childhood)
Rapid growth
Family history of thyroid cancer or MEN syndrome
Hoarseness / vocal cord paralysis
Dysphagia
Lymphadenopathy on exam

ATA 2009

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<td>Recommendation B</td>
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Korean Guidelines 2011
Moon et al,
Korean J Radiology 2011
NCI: Thyroid Nodule FNA - Conclusions

- 1. All focal 18FDG-PET-avid lesions should undergo FNA.
- 2. All hot nodules detected on sestamibi scans should undergo FNA.
- 3. Incidentalomas detected by (carotid) US should undergo a dedicated thyroid sonographic evaluation.
- 4. Until more data are available, incidentalomas seen on CT or MRI should undergo a dedicated thyroid sonographic evaluation.
- 5. Any nodule with sonographically suspicious features should be considered for FNA.
- 6. Lesions with a maximum diameter greater than 1.0-1.5 cm should be considered for FNA.

ATA 2009

- Suspicious Sonographic Features
  - Microcalcifications
  - Hypoechoic
  - Increased nodular vascularity
  - Infiltrative margins
  - Taller than wide on transverse view
Comet Tail Artifact

Benign Colloid Nodule

Microcalcification vs Comet Tail
Spongiform Echotexture

Note: Bright Linear Reflectors all posterior to the microcystic areas

PTC – Hypoechoic & Irregular Borders
Invasion of Strap Muscle

Intranodular Flow

B-Mode  Power Doppler
Multinodular Goiter: Characteristics matter more than Size

These hypoechoic nodules have similar appearances.....

Benign Hyperplastic Nodule

Papillary Thyroid Cancer

US cannot readily distinguish – need FNA
Bethesda Classification for Thyroid Cytopathology

### Bethesda System for Reporting Thyroid FNA Interpretations

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Prevalence</th>
<th>Risk of Malignancy</th>
<th>Usual Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient for Diagnosis</td>
<td>7%</td>
<td>1-4%</td>
<td>Repeat FNA with ultrasound guidance</td>
</tr>
<tr>
<td>Benign</td>
<td>66%</td>
<td>0-3%</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Atypical Cells of Undetermined Significance</td>
<td>4%</td>
<td>~5-10%</td>
<td>Repeat FNA</td>
</tr>
<tr>
<td>Suspicious for a Follicular Neoplasm</td>
<td>9%</td>
<td>15-30%</td>
<td>Lobectomy and decision vs. TTx based on pathologic diagnosis</td>
</tr>
<tr>
<td>Suspicious for a Hürthle Cell Neoplasm</td>
<td></td>
<td>15-45%</td>
<td>Lobectomy and decision vs. TTx based on pathologic diagnosis</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>9%</td>
<td>60-75%</td>
<td>NITx or Tx if lymphoma – repeat FNA for Flow Cytometry</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TTx</td>
</tr>
<tr>
<td>Malignant</td>
<td>5%</td>
<td>97-99%</td>
<td>TTx</td>
</tr>
</tbody>
</table>

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38yo Male Firefighter

- 38yo male without symptoms undergoes screening thyroid ultrasound as part of annual county firefighter health maintenance
- No risk factors for thyroid cancer
38yo Male Firefighter

- Cytology shows microfollicular pattern with no colloid: “suspicious for follicular neoplasm”
- TSH is 1.8 – should we do an I-123 scan?

I-123 Imaging

- Limited role in routine evaluation of nodules
- Primary use is to identify a clearly “hot” nodule
  - About 4-5% of all nodules
  - Very low risk of malignancy
- Consider if TSH low
  - Do not take patient off LT4 – scan not indicated
- No longer routinely used for follicular lesion evaluation
38yo Male Firefighter

- Cytology shows microfollicular pattern with no colloid: “suspicious for follicular neoplasm”
- TSH is 1.8 – should we do an I-123 scan? NO
- Role of molecular marker testing?
  - Which type of testing?

### Commercially Available
FNA Derived Molecular Markers

- Mutation/Translocation Panel
  - mirInform™ Thyroid - Asuragen
  - Comprehensive Thyroid Cancer Testing – Quest
- Gene Expression Classifier (exon array)
  - Afirma® Thyroid FNA Analysis - Veracyte
## Thyroid Tumor Signaling MAPK

### Molecular Markers

**Papillary Thyroid Cancer**
- RET/PTC: 15%
- Ras: 10-15%
- MEK-ERK

**Follicular Thyroid Cancer**
- Pax8-PPARγ: 20-40%
- BRAF: 40-60%

**Tumor growth, invasion, dedifferentiation**

### Gene-Derived/DNA Mutation Markers and RNA Fusion Transcripts (miRInform)

<table>
<thead>
<tr>
<th>DNA Mutation Markers</th>
<th>RNA Fusion Transcripts</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>RET/PTC1</td>
</tr>
<tr>
<td>G12R</td>
<td>V600E</td>
</tr>
<tr>
<td>G12V</td>
<td>Q61L</td>
</tr>
<tr>
<td>G13D</td>
<td>G12V</td>
</tr>
<tr>
<td>G12D</td>
<td>Q61R</td>
</tr>
<tr>
<td>G12A</td>
<td>Q61K</td>
</tr>
<tr>
<td>G12C</td>
<td></td>
</tr>
<tr>
<td>G12S</td>
<td></td>
</tr>
</tbody>
</table>
## Indeterminate (Follicular) Thyroid Nodule FNAs and Utility of Molecular Markers

**Independent study showing performance of mutational analysis on indeterminate FNAs**

<table>
<thead>
<tr>
<th>Atypia or Follicular lesions of undetermined significance (n=247)</th>
<th>Sensitivity 63%</th>
<th>Specificity 99%</th>
<th>PPV 88%</th>
<th>NPV 94%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation Positive (n=25)</td>
<td>Histology Malignant (n=35)</td>
<td>Histology Benign (n=212)</td>
<td>16 RAS (16 PTC, 1 FTC, 1 FC)</td>
<td>3 RAS (3 FA)</td>
</tr>
<tr>
<td></td>
<td>5 BRAF (6 PTC, 1 FTC, 1 FC)</td>
<td>1 PMK/RPPMG (1 FTC, 1 FC)</td>
<td>13 (11 PTC, 9 FTC, 2 FTC)</td>
<td>209 (166 HN, 43 FA)</td>
</tr>
<tr>
<td>Mutation Negative (n=222)</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Follicular or Hürthle cell neoplasm/Suspicious for follicular neoplasm (n=214)**

<table>
<thead>
<tr>
<th>Mutation Positive (n=13)</th>
<th>Histology Malignant (n=58)</th>
<th>Histology Benign (n=156)</th>
<th>Sensitivity 57%</th>
<th>Specificity 97%</th>
<th>PPV 87%</th>
<th>NPV 86%</th>
<th>Accuracy 86%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 BRAF (2 FTC, 1 PTC, 1 FTC)</td>
<td>7 RAS (6 FTC, 1 FTC)</td>
<td>29 RAS (2 FTC, 6 FTC)</td>
<td>2 PMK/RPPMG (2 FTC, 1 FTC)</td>
<td>25 (16 FTC, 8 FTC, 6 FTC)</td>
<td>151 (95 HN, 56 FA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation Negative (n=176)</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Suspicious for malignant cells (n=52)**

<table>
<thead>
<tr>
<th>Mutation Positive (n=20)</th>
<th>Histology Malignant (n=28)</th>
<th>Histology Benign (n=24)</th>
<th>Sensitivity 68%</th>
<th>Specificity 96%</th>
<th>PPV 95%</th>
<th>NPV 72%</th>
<th>Accuracy 81%</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 BRAF (10 FTC)</td>
<td>2 RAS (1 FTC, 1 FTC)</td>
<td>10 RAS (9 FTC, 1 FTC)</td>
<td>1 PMK/RPPMG (1 FTC)</td>
<td>1 RET/PTC (1 FTC)</td>
<td>9 (7 FTC, 2 FTC)</td>
<td>23 (17 HN, 6 FA)</td>
<td></td>
</tr>
<tr>
<td>Mutation Negative (n=32)</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Outside data:

FNA “atypical”  
CNBx “benign”  
**What next?**
FNA “atypical”  
CNBx “benign”

**EXPERT SECOND OPIN ON CYTOPATH: SUSP FOR PTC**  
**REPEAT FNA FOR MOLECULAR MARKER: BRAF POSITIVE**

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**Pivotal Independent Validation of the Gene Expression Classifier**  
(GEC – Afirma) Study Results

- Prospective, multicenter, double blind study at 49 sites across 26 US states.
- FNA samples collected from 3,789 unique patients.
- 567 indeterminate nodules, 387 patients operated, and final 265 eligible.
- At a 24% risk of malignancy in community practice, the NPV is 95%.

<table>
<thead>
<tr>
<th>GEC Result</th>
<th>Malignant Reference Standard (n=85)</th>
<th>Benign Reference Standard (n=180)</th>
<th>Study</th>
<th>Clinical Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspicious</td>
<td>78</td>
<td>87</td>
<td>Sensitivity</td>
<td>92%</td>
</tr>
<tr>
<td>Benign</td>
<td>7</td>
<td>93</td>
<td>Specificity</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PPV</td>
<td>47%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NPV</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Malignancy Prevalence</td>
<td>32%</td>
</tr>
</tbody>
</table>

60yo Dentist

Normal Thyroid Function
FNA “Susp for Follicular Neoplasm”
Left Lobe Normal
No Lymph Nodes
What Next?

AFIRMA “Suspicious” – Surgery: FVPTC

UTILITY OF FNA DERIVED MOLECULAR MARKERS FOR OPTIMIZATION OF INDETERMINATE THYROID NODULE MANAGEMENT

Jameson JL, NEJM 2012
UTILITY OF FNA DERIVED MOLECULAR MARKERS FOR OPTIMIZATION OF INDETERMINATE THYROID NODULE MANAGEMENT

Figure 1. Algorithm for Evaluating Thyroid Nodules. (MODIFIED) January 1, 2012

ATA Guidelines 2009
WORKUP OF THYROID NOGGLE DETECTED BY PALPATION OR IMAGING

THYROID Volume 19 (11) 2009 © American Thyroid Association
Thyroid Nodule with Cervical Lymphadenopathy

Thyroid ultrasound should always include evaluation of the neck for abnormal lymph nodes.

When abnormal lymph nodes are present, biopsy for cytology and TG analysis should be performed at the same time as the nodule biopsy.
Preoperative Evaluation of Lateral Compartment

Discovery of this right lateral neck lymph node changes the surgery to include modified neck dissection.

FNA of LN for both cytology and Tg-washout (or calcitonin)
Pre-Op Ultrasound Map

Office-Based Ultrasound Guided FNA
Ultrasound to Guide FNA

- Ability to access non-palpable masses
- Target solid component of complex lesion
- Decrease the chance of insufficient material
- More sensitive than CT for characterizing lesion and more efficient than CT guided FNA for many lesions
- Thyroid, Salivary Lesions, Lymph Nodes and other Neck Masses – Same Techniques Apply

FNA versus UG-FNA
Thyroid Biopsies

<table>
<thead>
<tr>
<th># Nodules</th>
<th>Conventional</th>
<th>UG-FNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochand-Priollet</td>
<td>132</td>
<td>15 %</td>
</tr>
<tr>
<td>Takashimia</td>
<td>327</td>
<td>19 %</td>
</tr>
<tr>
<td>Danese</td>
<td>9683</td>
<td>8.7 %</td>
</tr>
<tr>
<td>Izquierdo</td>
<td>376</td>
<td>11.2 %</td>
</tr>
<tr>
<td>Carmeci</td>
<td>497</td>
<td>16 %</td>
</tr>
</tbody>
</table>

Inadequate FNA Biopsies
**Preparation**

- Explanation of the procedure
- Proper patient position
- Room set-up
- Anti-septic – alcohol, betadine
- Anesthesia
  - None, Ice, Ethyl Chloride, Lidocaine
- Anxiety – pre-medication seldom needed

**Anticoagulation**

- Bleeding complications are rare after thyroid nodule FNA
- Recent report in patients on aspirin, heparin, clopidogrel or coumadin undergoing neck FNA showed no increased bleeding risk
- If patient on anticoagulant, consider 10 minute observation for hematoma formation
- Color doppler to avoid/detect small vessels

Monitor Clearly In View

Parallel Approach

[Image not provided]
Perpendicular Approach
Diff-Quick Staining For ROSE
ROSE – Improving Adequacy
Witt & Schmidt, *Thyroid* Oct 8, 2012 (e-pub)

- Meta-Analysis of 71 relevant studies
- Average adequacy 83% increased to 92% with ROSE
- Sites with lower initial adequacy benefit most

Parathyroid Ultrasound

- Diagnosis of Primary Hyperparathyroidism is made biochemically
- Ultrasound may aid in the localization of the adenoma
- Usually no indication for FNA
  - Exception: Re-operative patient to confirm adenoma
  - Not for cytology, but for needle PTH washout
- Assess for thyroid nodules
Lymph Node FNA

- Cytology
- Needle Washouts
  - Thyroglobulin washout on FNA for patients with differentiated thyroid cancer
  - Calcitonin washout on FNA for patients with medullary thyroid cancer
  - These are especially important with cystic nodes
- Flow, Gram Stain/Cx, AFB, IHC, etc as indicated
- Physician is not a technician – anytime an FNA is ordered, the entire neck should be evaluated
- Better surgical planning – it’s not ideal to be surprised when the excision of a lymph node reveals carcinoma!
FNA Flow Cytometry Diagnosis
Angioimmunoblastic T Cell Lymphoma

Parotid Mass

Warthin's Tumor
Palpable R neck Mass

FNA – Epidermal Inclusion Cyst

Practical Points

- Ultrasound with linear probe (7.5-12.5MHz) and doppler capability as well as digital archiving
- Local anesthesia optional
- Good communication with cytopathologist is critical
- On-site adequacy assessment can significantly decrease frequency of inadequate samples
- Thyroid – 27g needles used
Ultrasound Codes

- 76536 – Diagnostic ultrasound of neck soft tissues
- 79462 – Use of ultrasound for needle guidance
- 10022 – Ultrasound guided FNA
- 10021 – Non-US-guided FNA
- 88172 – Cytology adequacy assessment
- 88173 – Repeat Adequacy (if indicated)

Certification

- ACS offers courses for surgeons in ultrasound
- We anticipate that certification will be a requirement for reimbursement in the future
- Facility accreditation for ultrasound (through AIUM for example) will also likely be required
Thank You!