Thyroid Nodule Management

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Objectives

- Understand the appropriate diagnostic evaluation of thyroid nodules
- Recognize nodules which merit further evaluation with ultrasound guided fine needle aspiration (FNA)
- Understand utility of ancillary testing for nodules which are indeterminate on cytology
Prevalence depends on population and method of detection

- U.S. population ages 30-60 yrs, 6.4% of women and 1.5% of men possess palpable thyroid nodules
- Finnish population ages 19-60 yrs, 27% possess thyroid nodules via neck ultrasound
- 60% of the elderly (>70 yrs) possess nonpalpable thyroid nodules on autopsy
Thyroid Nodule Prevalence

Mazzaferri E, NEJM. 1993; 328:553-559.

Ultrasound or Autopsy

Palpation
Diagnostic Evaluation

• Physical examination
• Thyroid imaging
  – Neck ultrasound
  – Thyroid uptake and scan
• Laboratory testing
• Fine needle aspiration
• Helpful in differentiating non-thyroidal from thyroidal lesions
• Limited value in differentiating benign from malignant thyroid nodules
  – Firm, fixation to adjacent structures and concomitant cervical lymphadenopathy
• Thyroid “nodules” may NOT be true nodules
Diagnostic Evaluation
Thyroid/neck Ultrasound

ISTHMUS

1 L 0.35 cm
“Multinodular” Goiter
• What is the thyroid function?
  – TSH and free T4
Diagnostic Evaluation

**Low TSH**
-\(^{123}\)I Thyroid Uptake/Scan
  - Hyperfunctioning “Hot” Nodule
    - Treat Hyperthyroidism
  - Nonfunctioning “Cold” Nodule
    - Ultrasound and Fine Needle Aspiration (*if clinically indicated)

**Normal TSH**
- Yes
  - Nodule Initially Detected via Ultrasound?
    - Yes
      - Evaluate/Treat Hypothyroidism
    - No
      - Nodule Still Present w/ Palpation?
        - Yes
          - Continue to Treat Hypothyroidism
        - No
          - Ultrasound and Fine Needle Aspiration (*if clinically indicated)

**High TSH**
- Yes
  - Nodule Initially Detected via Ultrasound?
    - Yes
      - Evaluate/Treat Hypothyroidism
    - No
      - Continue to Treat Hypothyroidism

**CASE #1:** 62 yo M presents to establish care with a new physician. He has no acute complaints, but reports mild fatigue and occasional insomnia on review of systems.

**PMHx:** colitis, “thyroid problem many years ago”

**PSHx/FmHx/SoHx:** Noncontributory.

**Medications:** Asacol

**Physical Examination:** 160/80 120
anxious w/pressured speech
slight stare, but no exophthalmous, lid lag, conjunctival injection, or periorbital edema
no diffuse thyromegaly, bruit, or thrill; + 3.5 cm right sided nodule lateral to larynx
which moved with swallowing
tachycardic with regular rhythm, no JVD or edema
warm/moist skin, no dermopathy or onycholysis
+peripheral tremor; hyperreflexic DTRs
Laboratory Evaluation:
TSH - <0.01 uIU/mL (0.3 – 5.0)
Free T4 - 4.2 ng/dL (0.73 – 1.84)
Total T3 - 570 ng/dL (60 -180)

What’s the next diagnostic step?
Diagnostic Evaluation

Low TSH

123I Thyroid Uptake/Scan

Hyperfunctioning "Hot" Nodule

Treat Hyperthyroidism

Normal TSH

Nonfunctioning "Cold" Nodule

Ultrasound and Fine Needle Aspiration (*if clinically indicated)

High TSH

Nodule Initially Detected via Ultrasound?

Evaluate/Treat Hypothyroidism

Nodule Still Present w/Palpation?

Yes

No

Yes

No

Continue to Treat Hypothyroidism

Case #1

Laboratory Evaluation:
TSH - <0.01 uIU/mL (0.3 – 5.0)
Free T4 - 4.2 ng/dL (0.73 – 1.84)
Total T3 - 570 ng/dL (60 -180)

\[^{123}\text{I} - 24 \text{ hour uptake} = 57\%\]
Case #1: Thyroid/neck Ultrasound

Right Transverse

Right Transverse with Doppler
Case #1: Thyroid/neck Ultrasound
Diagnostic Evaluation
Fine Needle Aspiration (FNA)

- Safe, inexpensive, and accurate
- Results dependent on adequacy of specimen and interpretation (expertise of those performing FNA and interpreting cytology)
- Significantly impacts management of thyroid nodular disease
<table>
<thead>
<tr>
<th>Series</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schnürer &amp; Widström, 1978</td>
<td>96</td>
<td>76</td>
<td>100</td>
<td>99.5</td>
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<tr>
<td>Löwhagen et al., 1979</td>
<td>91</td>
<td>69</td>
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<td>Gardiner et al., 1986</td>
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<td>91</td>
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<td>Abu-Nema et al., 1987</td>
<td>88</td>
<td>100</td>
<td>100</td>
<td>98.9</td>
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<td>Hawkins et al., 1987</td>
<td>86</td>
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<td>95.4</td>
<td>97.6</td>
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<td>Hall et al., 1989</td>
<td>84</td>
<td>90</td>
<td>98.7</td>
<td>97</td>
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<tr>
<td>La Rosa et al., 1991</td>
<td>98</td>
<td>98</td>
<td>98.3</td>
<td>97.3</td>
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<tr>
<td>Gharib &amp; Goellner, 1993</td>
<td>98</td>
<td>99</td>
<td>98</td>
<td>99.3</td>
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<td>Holleman et al., 1995</td>
<td>84</td>
<td>52</td>
<td>53</td>
<td>83</td>
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<tr>
<td>Leonard &amp; Melcher, 1997</td>
<td>88</td>
<td>78</td>
<td>46</td>
<td>97</td>
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<tr>
<td>Hamming et al., 1998</td>
<td>67</td>
<td>99</td>
<td>96</td>
<td>88</td>
</tr>
<tr>
<td>Baloch et al., 1998</td>
<td>92</td>
<td>84</td>
<td>73.3</td>
<td>98.7</td>
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</table>

## FNA Cytology
### Diagnostic Accuracy

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical Pathology</td>
<td>516</td>
<td>86</td>
<td>74</td>
<td>34</td>
</tr>
<tr>
<td>Surgical Path + U/S follow-up</td>
<td>1289</td>
<td>86</td>
<td>89</td>
<td>31</td>
</tr>
</tbody>
</table>

*7.5% of FNA’s were non-diagnostic*

Fine Needle Aspiration
Impact on Nodule Management

Thyroid Nodule Dilemma

- Thyroid nodules are extremely common, affecting nearly 50% by age 60
- Thyroid nodules are rarely cancerous (5-10%)
- The incidence of thyroid cancer appears to be increasing, particularly small cancers, which may not be significant in the long run

Do we evaluate all thyroid nodules with FNA?
How do we select or exclude nodules for evaluation?
## Sonographic Features of Malignancy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Malignant Nodules (n=360)</th>
<th>Benign Nodules (n=489)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly solid</td>
<td>354 (98.3%)</td>
<td>426 (87.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marked Hypoechogenicity</td>
<td>149 (41.4%)</td>
<td>38 (7.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spiculated margin</td>
<td>174 (48.3%)</td>
<td>40 (8.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Microcalcification</td>
<td>159 (44.2%)</td>
<td>45 (9.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Taller than wide</td>
<td>144 (40.0%)</td>
<td>42 (8.6%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

## Nodule Composition: Solid vs Cystic

<table>
<thead>
<tr>
<th>Composition</th>
<th>Benign</th>
<th>Malignant</th>
<th>Percent Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completely Solid</td>
<td>330</td>
<td>55</td>
<td>14.3</td>
</tr>
<tr>
<td>Predominantly Solid</td>
<td>209</td>
<td>24</td>
<td>10.3</td>
</tr>
<tr>
<td>Mixed Solid and Cystic</td>
<td>129</td>
<td>8</td>
<td>5.8</td>
</tr>
<tr>
<td>Predominantly Cystic</td>
<td>85</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Completely Cystic</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

$p < 0.01$

### Sonographic Features of Malignancy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio for Malignancy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly solid</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marked Hypoechogenicity</td>
<td>8.499</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spiculated margin</td>
<td>2.749</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Microcalcification</td>
<td>4.599</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Taller than wide</td>
<td>2.787</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Suspicious Ultrasound Characteristics

Right Transverse  Right Longitudinal
### Ultrasound Characteristics of *Benign* Nodules

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spongiform</td>
<td>10.4</td>
<td>99.7</td>
<td>45.0</td>
<td>98.1</td>
</tr>
<tr>
<td>Isoechoic</td>
<td>56.6</td>
<td>88.1</td>
<td>59.9</td>
<td>86.6</td>
</tr>
<tr>
<td>Spongiform and isoechoic</td>
<td>6.1</td>
<td>100</td>
<td>44.0</td>
<td>100</td>
</tr>
</tbody>
</table>

# Ultrasound Characteristics of Benign Nodules

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Total Nodules</th>
<th>Benign</th>
<th>Surgical Intervention Necessary</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spongiform</td>
<td>210</td>
<td>210</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cyst w/colloid clot</td>
<td>53</td>
<td>53</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Giraffe</td>
<td>23</td>
<td>23</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>“White knight”</td>
<td>17</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>197</td>
<td>157</td>
<td>17</td>
<td>23</td>
</tr>
</tbody>
</table>

- Negative Predictive Value 100%

Spongiform and Cystic Thyroid Nodules

Spongiform

Cystic
### Which nodules should be biopsied?

#### 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

<table>
<thead>
<tr>
<th>Sonographic Pattern</th>
<th>Estimated Risk of Malignancy, %</th>
<th>FNA Size Cutoff</th>
<th>Sonographic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>High suspicion</td>
<td>&gt;70-90</td>
<td>≥ 1 cm</td>
<td>• Solid hypoechoic nodule with one or more of the following: irregular margins, microcalcifications, taller than wide shape, rim calcification with extrusive soft tissue, evidence of extrathyroidal extension (ETE)</td>
</tr>
<tr>
<td>Intermediate suspicion</td>
<td>10-20</td>
<td>≥ 1 cm</td>
<td>• Solid hypoechoic nodule with smooth margins without microcalcifications, taller than wide shape, or ETE</td>
</tr>
<tr>
<td>Low suspicion</td>
<td>5-10</td>
<td>≥ 1.5 cm</td>
<td>• Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid area without microcalcification, irregular margin, taller than wide shape, or ETE</td>
</tr>
<tr>
<td>Very low suspicion</td>
<td>&lt;3</td>
<td>≥ 2 cm or observation without FNA</td>
<td>• Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate or high suspicion nodules</td>
</tr>
<tr>
<td>Benign</td>
<td>&lt;1</td>
<td>No FNA</td>
<td>• Purely cystic nodules (no solid component)</td>
</tr>
</tbody>
</table>

Which nodules should be biopsied?

Diagnostic Categories
Thyroid Nodule Cytology

• Benign (60-70%)
• Indeterminate (15-20%)
• Malignant (5%)
  – Primary Thyroid Cancer
  – Metastatic Cancer
  – Lymphoma
• Nondiagnostic (10%)
Bethesda System for Thyroid Cytology

- Benign
- Atypia of undetermined significance (or Follicular lesion of undetermined significance)
- Follicular neoplasm (or Suspicious for follicular neoplasm)
- Suspicious for malignancy
- Malignant
- Non-diagnostic/Unsatisfactory

## The Bethesda System

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Malignancy (%)</th>
<th>Recommended Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>0-3</td>
<td>Clinical Follow-up</td>
</tr>
<tr>
<td>(F)LUS</td>
<td>5-15</td>
<td>Repeat FNA</td>
</tr>
<tr>
<td>Follicular lesion</td>
<td>15-30</td>
<td>Surgical lobectomy</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>60-75</td>
<td>Near-total thyroidectomy</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99</td>
<td>Near-total thyroidectomy</td>
</tr>
<tr>
<td>Non-diagnostic/Unsat.</td>
<td>1-4</td>
<td>Repeat FNA with u/s guidance</td>
</tr>
</tbody>
</table>

## The Bethesda System

### Implied Risk of Malignancy and Recommended Clinical Management

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Malignancy (%)</th>
<th>Recommended Management</th>
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<tr>
<td>Benign</td>
<td>0-3</td>
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<tr>
<td>Malignant</td>
<td>97-99</td>
<td>Near-total thyroidectomy</td>
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<tr>
<td>Non-diagnostic/Unsat.</td>
<td>1-4</td>
<td>Repeat FNA with u/s guidance</td>
</tr>
</tbody>
</table>

“Historical” Cytology Management Algorithm

- **Benign**
  - Surveillance

- **Indeterminate**
  - Follicular lesion of undetermined significance (F) LUS
  - Follicular or Oncocytic lesion
  - Suspicious for malignancy
  - Repeat FNA versus Surgery?

- **Malignant**
  - Total Thyroidectomy

- **Non-diagnostic**
  - Repeat FNA w/Ultrasound
  - Diagnostic?
    - No
    - Yes
      - See Above
"Historical" Cytology Management Algorithm

**Indeterminate Lesions**

- **Follicular Lesion of Undetermined Significance (F)LUS**
- **Follicular or Oncocytic Lesion**
- **Suspicious for Papillary Thyroid Carcinoma**

**Risk of Thyroid Cancer**

- 5-15%
- 15-30%
- 60-75%

**Treatment Approach**

- Repeat FNA
- Hemithyroidectomy
- Total Thyroidectomy
MAPK Signaling Pathway

Nikiforov, Y. Mod Path. 2008, 21:S37-43
### Frequent Molecular Mutations in Differentiated Thyroid Cancer

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Papillary Carcinoma</strong></td>
<td></td>
</tr>
<tr>
<td><em>BRAF</em></td>
<td>45</td>
</tr>
<tr>
<td><em>RET/PTC</em></td>
<td>20</td>
</tr>
<tr>
<td><em>RAS</em></td>
<td>10</td>
</tr>
<tr>
<td><strong>Follicular Carcinoma</strong></td>
<td></td>
</tr>
<tr>
<td><em>RAS</em></td>
<td>45</td>
</tr>
<tr>
<td><em>PAX8-PPARY</em></td>
<td>35</td>
</tr>
</tbody>
</table>

Nikiforov, Y. Mod Path. 2008, 21:S37-43
# +BRAF Specificity in Indeterminate Cytology

<table>
<thead>
<tr>
<th></th>
<th>BRAF</th>
<th>Thyroid CA</th>
<th>Adenoma</th>
<th>Goiter</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xing M, 2004</td>
<td>2/25</td>
<td>2/13</td>
<td>0/4</td>
<td>0/7</td>
<td>0/1</td>
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<tr>
<td>Cohen Y, 2004</td>
<td>23/91</td>
<td>23/59</td>
<td>-/-</td>
<td>-/-</td>
<td>0/32</td>
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<tr>
<td>Salvatore G, 2004</td>
<td>4/11</td>
<td>4/11</td>
<td>0</td>
<td>0</td>
<td>-/-</td>
</tr>
<tr>
<td>Rowe LR, 2006</td>
<td>3/19</td>
<td>3/19</td>
<td>0</td>
<td>0</td>
<td>-/-</td>
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<tr>
<td>Sapio MR, 2007</td>
<td>4/36</td>
<td>4/8</td>
<td>-/-</td>
<td>-/-</td>
<td>0/28</td>
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<tr>
<td>Marchetti I, 2009</td>
<td>18/52</td>
<td>18/33</td>
<td>-/-</td>
<td>0/19</td>
<td>-/-</td>
</tr>
<tr>
<td>Jo YS, 2009</td>
<td>7/24</td>
<td>7/9</td>
<td>-/-</td>
<td>-/-</td>
<td>0/15</td>
</tr>
<tr>
<td>Zatelli, MC, 2009</td>
<td>11/107</td>
<td>11/31</td>
<td>0/74</td>
<td>-/-</td>
<td>0/2</td>
</tr>
<tr>
<td><strong>Totals (2004-09)</strong></td>
<td><strong>72/365</strong></td>
<td><strong>72/183</strong></td>
<td><strong>0/78</strong></td>
<td><strong>0/26</strong></td>
<td><strong>0/78</strong></td>
</tr>
</tbody>
</table>

Positive Predictive Value of +BRAF = 100% (72/72)
### +BRAF Specificity ALL Nodules

<table>
<thead>
<tr>
<th>Study</th>
<th>BRAF</th>
<th>Thyroid CA</th>
<th>Adenomas</th>
<th>Goiter</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xing M, 2004</td>
<td>8/40</td>
<td>8/23</td>
<td>0/4</td>
<td>0/10</td>
<td>0/3</td>
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<tr>
<td>Cohen Y, 2004</td>
<td>5/55</td>
<td>5/32</td>
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<td>-/-</td>
<td>0/23</td>
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<td>Salvatore G, 2004</td>
<td>26/96</td>
<td>26/69</td>
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<td>Domingues R, 2005</td>
<td>3/24</td>
<td>3/13</td>
<td>0/5</td>
<td>0/6</td>
<td>0/0</td>
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<tr>
<td>Rowe LR, 2006</td>
<td>3/19</td>
<td>3/19</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
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<td>Jin L, 2006</td>
<td>31/71</td>
<td>31/61</td>
<td>0/6</td>
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<td>0/3</td>
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<tr>
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<td>-/-</td>
<td>-/-</td>
<td>-/-</td>
<td>0/46</td>
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<tr>
<td>Marchetti I, 2009</td>
<td>-/-</td>
<td>0/19</td>
<td>-/-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jo YS, 2009</td>
<td>-/-</td>
<td>-/-</td>
<td>0/15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zatelli, MC, 2009</td>
<td>-/-</td>
<td>-/-</td>
<td>0/4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Totals (2004-09)</strong></td>
<td><strong>217/691</strong></td>
<td><strong>217/445</strong></td>
<td><strong>0/108</strong></td>
<td><strong>0/44</strong></td>
<td><strong>0/94</strong></td>
</tr>
</tbody>
</table>

**100% Positive Predictive Value**
Follicular Lesion of Undetermined Significance (F)LUS

Follicular or Oncocytic Lesion

Suspicious for Papillary Thyroid Carcinoma

Risk of Thyroid Cancer

Molecular Marker Testing BRAF

- 5-15%
- 15-30%
- 60-75%
- 100%

Treatment Approach

Repeat FNA

Hemithyroidectomy

Total Thyroidectomy

Total Thyroidectomy

Total Thyroidectomy

Risk of Thyroid Cancer

- ++
+ --
+ --
+ +

Treatment Approach

Repeat FNA

Hemithyroidectomy

Total Thyroidectomy

Total Thyroidectomy

Total Thyroidectomy

Risk of Thyroid Cancer

- ++
+ --
+ --
+ +
Current Mutations in Differentiated Thyroid Cancer

- **BRAF**: 70%
- **RAS**: 11%
- **PAX8/PPARγ**: 9%
- **RET/PTC1**: None
- **RET/PTC3**: None
- **BRAF rearrangements**: 70%
- **Novel mutations**: 9%
- **Novel rearrangements**: 11%

Courtesy of Yuri E. Nikiforov, MD
Follicular Lesion Cytology w/Negative Mutational Testing

Follicular Lesion Cytology w/Negative Mutational Testing

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Malignant</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-) Negative Mutation</td>
<td>101</td>
<td>4</td>
<td>97</td>
</tr>
<tr>
<td>(+) Positive Mutation</td>
<td>42</td>
<td>35</td>
<td>7</td>
</tr>
</tbody>
</table>

PPV 83% (CI: 72-95%)
**NPV 96% (CI: 92-95%)**
Accuracy 92% (CI 88-97%)
Indeterminate Lesions

- Follicular Lesion of Undetermined Significance F(LUS)
- Follicular or Oncocytic Lesion
- Suspicious for Papillary Thyroid Carcinoma

**Risk of Thyroid Cancer**

- 5-15%
- 20-30%
- 50-75%

**Negative Molecular Marker Testing**

- 4%

**Treatment Approach**

- Ultrasound Follow-up
Utility of Molecular Testing


- Molecular Markers
Questions?