Objectives

• Review updated recommendations for evaluating thyroid nodules by ultrasound and biopsy
• Understand the evolving role of molecular testing in the evaluation of thyroid nodules
• Determine how to monitor benign thyroid nodules
• (No conflicts of interest)
Why do we care about thyroid nodules?

- They are extremely common – you will see them every day in your practice.
- They can harbor thyroid cancer, but thyroid cancer is uncommon.
- We need a cost-effective way to find uncommon cancers in common nodules.

What’s new about thyroid nodules?

- New recommendations for evaluating and treating thyroid nodules (Alexander, Thyroid 26:1-133, 2016)
- Decide which nodules to biopsy based on US characteristics, not just on size (fewer biopsies)
- New cytopathology classification system
- Molecular testing of nodules (fewer surgeries)
- Monitor, do not treat, benign nodules
Case Report

A healthy 47 year old woman reports for her yearly gynecologic exam. She has no complaints.

On PE, she has a 3 cm mobile, soft left lower pole thyroid nodule. The rest of the gland feels normal, and there is no adenopathy.

Question:

How should this patient be evaluated?
Case Report

A healthy 58 year old man is noted to have an asymptomatic left carotid bruit at his annual exam. US shows a carotid plaque, and incidentally reports a 2 cm thyroid nodule.

On PE, the thyroid gland feels normal, and there is no adenopathy.

Question:
How should this patient be evaluated?

Prevalence of Thyroid Nodules

- 4-7% of adults have palpable thyroid nodules
- Increased prevalence in women, older patients, history of radiation exposure, iodine deficiency

Mazzaferri, 1993
Prevalence of Thyroid Nodules

- 4-7% of adults have palpable thyroid nodules
- Increased prevalence in women, older patients, history of radiation exposure, iodine deficiency
- 30-40% have nonpalpable thyroid nodules

Mazzaferri, 1993

Incidence and Mortality Trends in Thyroid Cancer

Lim JAMA 2017
Prevalence of Clinically Relevant Thyroid Nodules

- 5-10% of nodules are malignant (regardless of size, location, palpable or not)
- Thyroid cancer becomes clinically relevant at 1 cm
- Most clinically relevant nodules are > 1 cm

Only a fraction of thyroid nodules are > 1 cm

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### Prevalence of thyroid nodules in the general population

<table>
<thead>
<tr>
<th>Method</th>
<th>All nodules</th>
<th>Nodules &gt; 1 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>By palpation</td>
<td>4-7%</td>
<td>1-3%</td>
</tr>
<tr>
<td>By ultrasound</td>
<td>30-40%</td>
<td>3-8%</td>
</tr>
</tbody>
</table>
Thyroid Nodules in MNG

1985 patients had US for thyroid nodules
3483 nodules > 1 cm
All nodules had FNA

• Biopsy of dominant nodule misses 28% of cancers
• Conclusion: do not prioritize solely by which nodule is largest

1181 solitary

\[ \downarrow \]

Cancer in 15% of patients

2302 in MNG

\[ \downarrow \]

Cancer in 15% of patients (independent of # of nodules)

Worrisome Features of Thyroid Nodules

Clinical
• Male gender
• Hoarseness, dysphagia
• Rapid growth
• Hx of radiation exposure
• Family history
• Abnormal lymph nodes
• Hashimoto’s thyroiditis (lymphoma)

Ultrasound
• Solid or mostly solid
• Taller than wide
• Hypoechoic
• Microcalcifications
• Irregular margins
• Intranodular vascularity
• Signs of extra-thyroidal extension
• Suspicious LN

None of these are specific for cancer:
Pathologic examination is almost always required to diagnose thyroid cancer.
Evaluation of Thyroid Nodules

TSH, Neck ultrasound (thyroid and LN)

Nonsuppressed TSH, single or multiple nodules

Suppressed TSH, single or multiple nodules

↓

Biopsy larger or suspicious nodules

I-123 thyroid scan

Palpable nodule

Nonpalpable nodule

carotid

trachea

trachea
Palpable “nodule” in Hashimoto’s
2016 ATA Guidelines for US-Guided FNA of Thyroid Nodules

<table>
<thead>
<tr>
<th>Sonographic pattern</th>
<th>Estimated risk of malignancy</th>
<th>FNA size cutoff (largest dimension)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High suspicion</td>
<td>&gt; 70-90%</td>
<td>≥ 1 cm</td>
</tr>
<tr>
<td>Intermediate suspicion</td>
<td>10-20%</td>
<td>≥ 1 cm</td>
</tr>
<tr>
<td>Low suspicion</td>
<td>5-10%</td>
<td>≥ 1.5 cm</td>
</tr>
<tr>
<td>Very low suspicion</td>
<td>&lt; 3%</td>
<td>Consider if ≥ 2.0 cm Or observe</td>
</tr>
<tr>
<td>Benign</td>
<td>&lt; 1%</td>
<td>No FNA</td>
</tr>
</tbody>
</table>

The Evaluation of Thyroid Nodules - ATA Guidelines 2016 -

- Perform thyroid US in all patients with suspected thyroid nodules
- Perform US-guided FNA of selected nodules
  - Exact size cut-off depends on US features
- In MNG, prioritize nodules based on US characteristics, and preferentially aspirate those with a suspicious sonographic appearance.
- If none of the nodules in a MNG has a suspicious sonographic appearance, reasonable to only aspirate largest nodules.
Fine Needle Aspiration Biopsy of Thyroid Nodules

- Success rates (adequate biopsy) depend on:
  - US guidance
  - Experience of operator
  - Characteristics of lesion
  - Number of passes
  - Presence of a pathologist

- Low FN (1 – 6%) and FP (0.5 - 5%) rates
- Reduces surgery rates by > 50%
- Inadequate biopsies must be repeated (1-4% malignant)

Cytopathology of Thyroid FNAs

- In the past, there was significant variability in reporting cytological findings in thyroid FNA samples.
- 2007 NCI Thyroid Fine-Needle Aspiration State of the Science Conference
- Consensus recommendations: the Bethesda System for Reporting Thyroid Cytopathology
  - 6 categories, including nondiagnostic
FNA

Benign (colloid nodules, cysts etc.)
- 0-3% malignant

Malignant (usually papillary)
- 97-99% malignant

Suspicious
- 60-75% malignant

Follicular lesion undetermined significance
- 15-30% malignant
- 5-15% malignant

Indeterminate

Consider molecular testing
Surgery vs. Observe
Molecular Testing of Thyroid FNAs

Rule-In Test:
- Seven gene panel of genetic mutations and re-arrangements
- High positive predictive value (85-100%)
- Low negative predictive value

Rule-Out Test:
- Gene expression classifier using mRNA expression of 167 genes
- High negative predictive value (95%)
- Low positive predictive value (38%)

Both are new, with only short-term follow-up
Both are expensive (but could tailor surgery)

Evaluation of Thyroid Nodules

TSH, Neck ultrasound (thyroid and LN)

- Nonsuppressed TSH, single or multiple nodules
  - Biopsy nodules > 1-2 cm and suspicious nodules
  - I-123 Scan
    - Biopsy cold nodules per ATA guidelines
    - Treat hyperthyroidism

- Suppressed TSH, single or multiple nodules
Radionuclide Scans of Thyroid Nodules

- **Cold Nodule**
  - TSH = 1.2
  - Did not need scan
  - Needs FNA

- **Hot Nodule**
  - TSH = 0.01
  - Did need scan
  - Does not need FNA

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**Case Report – Cont.**

The 47 year old woman with a single palpable thyroid nodule has a thyroid ultrasound, which confirms a single, solid 3 cm. left thyroid nodule. FNA of the nodule is read as **benign**.

**Question:**

What is the optimal way to follow this nodule?
Treatment of Benign Thyroid Nodules

- Observation – usually recommended
- L-thyroxine suppression
  - No longer recommended
  - Poor efficacy
  - Risks of bone loss and atrial fibrillation
- Surgery - cosmetic issues, local symptoms, patient preference

Observation of Benign Thyroid Nodules

- Benign nodules tend to grow slowly over years
- Age, sex, TSH, L-T4 suppressive therapy do not predict growth
Observation of Benign Thyroid Nodules

- Repeat first US at 6-24 months, depending on US risk stratification (more important than gradual growth)
- Further US depending on US risk stratification (may change)
- Repeat FNA only in nodules that grow “significantly” or develop worrisome clinical or US features
- Significant growth = > 50% increase in volume (>20% increase in two dimensions), minimum increase 2 mm

What’s New in Thyroid Nodules

- The same evaluation is used for palpable and non-palpable thyroid nodules: TSH and ultrasound
- Prioritize nodules for FNA based on US characteristics as well as size
- Utilize a standard cytopathologic system (the Bethesda System)
- Molecular testing of thyroid FNA specimens will likely play an increasing role
- Monitor benign thyroid nodules rather than proceed to treatment, but don’t monitor too often