MANAGEMENT OF THYROID NODULES

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9/11/15
DISCLOSURES

- Nothing to disclose.
OBJECTIVES

- Overview of Thyroid Nodules
  - Demographics
  - Features of Nodules
- Workup
  - Ultrasound
  - Role of Biopsy (FNA, Core, Genetic Markers)
- Surveillance
- Thyroid Cancer
THYROID NODULE FACTS

- Prevalence of palpable nodules: 5% women, 1% men in iodine sufficient areas
- Ultrasound prevalence: 19-67%, higher women & elderly
- 2011 estimate of 350,000 new nodule diagnoses
- Approximately 95% are benign
- American Cancer Society estimates:
  - 62450 new thyroid cancer diagnoses in the US in 2015
  - 47230 women, 15220 men
  - 1950 thyroid cancer deaths in the US in 2015
Age-Adjusted SEER Incidence Rates
By Cancer Site
All Ages, All Races, Both Sexes
1975–2012 (SEER 9)

Cancer sites include invasive cases only unless otherwise noted.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups – Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 4.2.0, April 2015, National Cancer Institute.
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
CASE #1

- 30-year-old woman presents to clinic after her dentist noted a lump in her throat. She is asymptomatic and has no history of neck radiation. Neck exam is notable for a firm 2 x 2 cm left lobe nodule. Serum TSH is 1.1 mIU/mL.

Question: What is the appropriate next step?

- I-123 uptake and scan
- Trial of levothyroxine and TSH suppression
- FNA biopsy
- Ultrasound exam
- Follow up exam in one year
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**Appropriate Evaluation of Thyroid Nodule**

- Nodules are frequently incidentally noted during investigation of unrelated condition
  - Prevalence rate of a nodule on ultrasound of the neck 67%, CT or MRI of the neck 15%, FDG-PET 1-2%
  - FDG-PET avid lesions 30% malignant if focal uptake

- History:
  - Childhood head/neck irradiation
  - Total body irradiation for BMT
  - Family history of thyroid cancer or thyroid cancer syndrome (Cowden’s syndrome, familial polyposis, Carney complex, MEN2, Werner syndrome) in first degree relative
  - Exposure to ionizing radiation childhood/adolescence
CASE #1

Which is NOT a predictor of malignancy in this patient’s thyroid nodule?

- Serum TSH
- Serum calcitonin
- Nodule size and number
- History of childhood head-neck radiation
CASE #1

- Which is NOT a predictor of malignancy in this patient’s thyroid nodule?
  - Serum TSH
  - Serum calcitonin
  - Nodule size and number
  - History of childhood head-neck radiation

- Low TSH associated with hyperfunctional nodule
  - Low likelihood of malignancy

- Calcitonin marker for medullary thyroid cancer
  - (cancer of C-cells in thyroid)

- Childhood head-neck irradiation increases likelihood of malignancy
### Appropriate Evaluation of Thyroid Nodule

- **Physical Exam:**
  - Vocal cord paralysis?
  - Lateral cervical LN enlargement
  - Fixation of the nodule to surrounding tissues

- **Appropriate First Steps:**
  - Serum TSH
  - Ultrasound neck
  - If TSH below normal range, I-123 thyroid uptake and scan. If TSH normal, no need for uptake scan at this point. Hyperfunctioning nodules rarely malignant.
  - Serum thyroglobulin can be elevated in most thyroid diseases and, if even a portion of the thyroid is still intact, is an insensitive and nonspecific test for thyroid cancer so should not be used for screening.
  - If there is a family history of medullary thyroid cancer, calcitonin level may be useful but is not thought to be cost-effective as a screening tool.
CASE #2

- 47 year old male with a history of posterior neck pain related to a MVA. A CT in the ER revealed several thyroid nodules. He denies any radiation history, dysphagia, voice changes, family history of thyroid cancer.

- He is sent for a thyroid ultrasound as is noted to have three nodules:
  - 5 x 6 x 8 mm, isoechoic nodule with regular border and no microcalcifications or nodular blood flow
  - 10 x 12 x 16 mm predominantly cystic lesion
  - 12 x 12 x 16 mm hypoechoic nodule with irregular borders and mild intranodular blood flow
# Multinodular Goiter

<table>
<thead>
<tr>
<th>Study (yr, location)</th>
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<th>Cancer rate (single nodule)</th>
<th>Cancer rate (multiple nodules)</th>
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<td>Marqusee et al (2000 US)</td>
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## Ultrasound Features of Thyroid Nodules

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<td><strong>Taller than wide</strong></td>
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<td><strong>High stiffness</strong></td>
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Values represent n unless otherwise indicated. R = Retrospective; P = prospective.
**Ultrasound Features Abridged**

<table>
<thead>
<tr>
<th>Concerning</th>
<th>Typically Benign</th>
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<tbody>
<tr>
<td>Taller than wide</td>
<td>No signs of high suspicion</td>
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<tr>
<td>Irregular borders</td>
<td>Simple cyst</td>
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<tr>
<td>Microcalcifications</td>
<td>Spongiform nodule</td>
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<tr>
<td>Markedly hypoechoic</td>
<td>Isolated macrocalcification</td>
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<tr>
<td>Suspicious LN</td>
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<td>High stiffness elastography*</td>
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The bottom line: no single ultrasound characteristic is a slam dunk. So which nodules do you recommend for biopsy?
### Table 3. Sonographic and Clinical Features of Thyroid Nodules and Recommendations for FNA

<table>
<thead>
<tr>
<th>Nodule sonographic or clinical features</th>
<th>Recommended nodule threshold size for FNA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-risk history</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Nodule WITH suspicious sonographic features&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt;5 mm</td>
</tr>
<tr>
<td>Recommendation A</td>
<td></td>
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<tr>
<td>Nodule WITHOUT suspicious sonographic features&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt;5 mm</td>
</tr>
<tr>
<td>Recommendation I</td>
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<tr>
<td>Abnormal cervical lymph nodes</td>
<td>All&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Recommendation A</td>
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<tr>
<td>Microcalcifications present in nodule</td>
<td>≥1 cm</td>
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<tr>
<td>Recommendation B</td>
<td></td>
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<tr>
<td><strong>Solid nodule</strong></td>
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<tr>
<td>AND hypoechoic</td>
<td>&gt;1 cm</td>
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<tr>
<td>Recommendation B</td>
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<tr>
<td>AND iso- or hyperechoic</td>
<td>≥1–1.5 cm</td>
</tr>
<tr>
<td>Recommendation C</td>
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<tr>
<td><strong>Mixed cystic–solid nodule</strong></td>
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<tr>
<td>WITH any suspicious ultrasound features&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≥1.5–2.0 cm</td>
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<tr>
<td>Recommendation B</td>
<td></td>
</tr>
<tr>
<td>WITHOUT suspicious ultrasound features</td>
<td>≥2.0 cm</td>
</tr>
<tr>
<td>Recommendation C</td>
<td></td>
</tr>
<tr>
<td><strong>Spongiform nodule</strong></td>
<td>≥2.0 cm&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Recommendation C</td>
<td></td>
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<tr>
<td><strong>Purely cystic nodule</strong></td>
<td>FNA not indicated&lt;sup&gt;e&lt;/sup&gt;</td>
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<sup>a</sup>High-risk history: History of thyroid cancer in one or more first degree relatives; history of external beam radiation as a child; exposure to ionizing radiation in childhood or adolescence; prior hemithyroidectomy with discovery of thyroid cancer, <sup>18</sup>FDG avidity on PET scanning; MEN2/FMTC-associated RET protooncogene mutation, calcitonin >100 pg/mL. MEN, multiple endocrine neoplasia; FMTC, familial medullary thyroid cancer.

<sup>b</sup>Suspicious features: microcalcifications; hypoechoic; increased nodular vascularity; infiltrative margins; taller than wide on transverse view.

<sup>c</sup>FNA cytology may be obtained from the abnormal lymph node in lieu of the thyroid nodule.

<sup>d</sup>Sonographic monitoring without biopsy may be an acceptable alternative (see text) (48).

<sup>e</sup>Unless indicated as therapeutic modality (see text).
NEXT STEP - BIOPSY

- **Fine Needle Aspiration**
  - Aspiration of palpable nodule
- **FNA with Ultrasound Guidance**
  - Localization of nodule with ultrasound
  - Preferred for nonpalpable, posterior, small, mixed cystic/solid (allows to target solid component)
  - Repeat FNA following previous nondiagnostic biopsies
- **Core Biopsy**
  - Not currently in the guidelines by the ATA but has been proposed to be more accurate and more decisive, particularly if a previous nondiagnostic result. However, also with risk of more discomfort and not always feasible (small nodule near vascular structures).
- **Molecular Diagnostics**
  - RAS, BRAF, PAX8/PPARγ and RET/PTC genetic mutations and molecular alterations can be screened from a FNA tissue sample; starting to use this tool more, particularly in nondiagnostic previous biopsies
BIOPSY RESULTS

- Cytology Nondiagnostic:
  - Criteria for adequacy – six follicular groups, each containing 10-15 cells derived from at least two aspirates of a nodule
    - After an initial nondiagnostic cytology, repeat US FNA will yield a diagnostic cytology in 75% solid nodules and 50% cystic nodules
    - Up to 7% of nodules continue to yield nondiagnostic cytology
    - If two nondiagnostic studies, could consider surgery, particularly if nodule is solid

- Cytology PTC or suspicious for PTC:
  - Surgery recommended
  - Papillary thyroid cancer arises from follicular cells in the thyroid
  - PTC and related follicular thyroid cancer make up approximately 90% of thyroid cancers
**Biopsy Results**

- **Benign**
- **Indeterminate**
  - “Follicular neoplasm” or “Hürthle cell neoplasm” in 15-30% FNA samples and 20-30% risk of malignancy
  - “Atypia” or “Follicular lesion of undetermined significance” reported to have 5-10% risk of malignancy
  - ATA Guidelines suggest that further characterization by genetic marker screening may (expert opinion) be useful to further characterize these nodules.
  - “Suspicious for PTC” or “Hürthle cell neoplasm” lobectomy or total thyroidectomy recommended.
**But What About Multinodular Thyroid Glands?**

- Multiple thyroid nodules have the same risk of malignancy of those with solitary nodules.
- If 2+ thyroid nodules >1 cm, those with suspicious ultrasound features should be chosen for biopsy.
- If TSH low or low normal, could have a autonomous nodule. Could consider I-123 uptake and scan and preferential biopsy of cold nodules if present.
**Follow up of Nodules**

- All benign thyroid nodules: repeat ultrasound 6-18 months after initial FNA. If nodule stable (no more than 50% change in volume or <20% increase in two dimensions), can follow up again in 3-5 years OR if interval change in exam or symptoms.
- Evidence of nodule growth: repeat FNA, preferably with ultrasound guidance.
- Cystic nodules can be drained for symptomatic relief but recurrence not uncommon (60-90%)
SPECIAL CASES

- **Children:**
  - Nodules less frequent than in adults (one study 20/1000 children with palpable nodule)
  - Diagnosis/therapy is the same for children as adults

- **Pregnant Women:**
  - If TSH suppressed, can defer biopsy until after pregnancy and breastfeeding and then proceed with I-123 uptake and scan
  - In areas of mild-to-moderate iodine deficiency, several studies suggested some increase in size of nodules during pregnancy.
  - Still unclear if frequency of thyroid cancer in women is higher if nodule detected during pregnancy.
  - Same recommendations for ultrasound and FNA if indicated in pregnant woman.
  - If PTC, surgery second trimester.
  - NO I-123 or I-131 during pregnancy.
FIG. 1. Algorithm for the evaluation of patients with one or more thyroid nodules.

*If the scan does not show uniform distribution of tracer activity, ultrasound may be considered to assess for the presence of a cystic component.
REFERENCES

- Cooper et al. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2009.
- Duick et al. The Impact of Benign Gene Expression Classifier Test Results on the Endocrinologist-Patient Decision to Operate on Patients with Thyroid Nodules with Indeterminate Fine-Needle Aspiration Cytology. Thyroid 2012.
- Stagnaro-Green et al. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum. Thyroid 2011.
I grew up in Olympia, Washington and attended Pacific Lutheran University, completing a BS in Biology in 1989.

I worked for two years as a research technician before I attended Oregon State University as a graduate student. August 1997, I completed my PhD in Molecular and Cellular Biology. My interests included neuropharmacology and molecular mechanisms of neurotransmitter action.

I moved to Charlottesville, Virginia for my postdoctoral fellowship and studied the neuroanatomy of adenosine receptors.

I went to medical school at University of Virginia and developed an interest in Endocrinology on one my first clinical rotations.

I moved back to the Pacific NW in 2004 and attended residency in Internal Medicine and fellowship in Endocrinology at OHSU.

I started with Portland Diabetes and Endocrinology Center in 2011 after completing fellowship.

I enjoy being in the NW, close to my family and near the mountains, river, hiking trails and the ocean.