THYROID NODULES: WHEN TO REFER
“THE GOOD, BAD AND THE UGLY”

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- N/A
QUESTIONS REGARDING THYROID NODULES

1. What is the appropriate evaluation of clinically or incidentally discovered thyroid nodule(s)?
2. What laboratory tests and imaging modalities are indicated?
3. What is the role of fine-needle aspiration (FNA)?
4. What is the best method of long-term follow up of patients with thyroid nodules?
5. What is the role of medical therapy of patients with benign thyroid nodules?
6. How should thyroid nodules in children and pregnant women be managed?
7. WHEN TO REFER?
Basic Thyroid Anatomy
Some necks are more difficult to examine than others: **History & Physical!**
THE THYROID EXAM

All Thumbs? You’re not alone!

If you can feel it - then it likely shouldn’t be there!
46% of nodules > 1 cm on ultrasound, escape clinical detection

in NA, 50-67% asymptomatic thyroid nodules found at autopsy

in areas not affected by nuclear fall-out, the annual incidence of thyroid cancer is 1.2 to 2.6 cases per 100,000 in men and 2.0 to 3.8 cases per 100,000 in women
PATHOPHYSIOLOGY OF THYROID NODULES

Benign 85-95%

Malignant 5-15%

CLASSIFICATION OF THYROID NEOPLASMS

<table>
<thead>
<tr>
<th>Classification</th>
<th>Approximate Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign</strong></td>
<td></td>
</tr>
<tr>
<td>Follicular epithelial cell adenomas</td>
<td></td>
</tr>
<tr>
<td>Macrofollicular (colloid)</td>
<td></td>
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<tr>
<td>Normofollicular (simple)</td>
<td></td>
</tr>
<tr>
<td>Microfollicular (fetal)</td>
<td></td>
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<tr>
<td>Trabecular (embryonal)</td>
<td></td>
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<tr>
<td>Hürthle cell variant (oncocytic)</td>
<td></td>
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<tr>
<td><strong>Malignant</strong></td>
<td></td>
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<tr>
<td>Follicular epithelial cell</td>
<td></td>
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<tr>
<td>Well-differentiated carcinomas</td>
<td></td>
</tr>
<tr>
<td>Papillary carcinomas</td>
<td>80-90</td>
</tr>
<tr>
<td>Pure papillary</td>
<td></td>
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<tr>
<td>Follicular variant</td>
<td></td>
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<tr>
<td>Diffuse sclerosing variant</td>
<td></td>
</tr>
<tr>
<td>Tall cell, columnar cell variants</td>
<td></td>
</tr>
<tr>
<td>Follicular carcinomas</td>
<td>5-10</td>
</tr>
<tr>
<td>Minimally invasive</td>
<td></td>
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<tr>
<td>Widely invasive</td>
<td></td>
</tr>
<tr>
<td>Hürthle cell carcinoma (oncocytic)</td>
<td></td>
</tr>
<tr>
<td>Insular carcinoma</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated (anaplastic) carcinomas</td>
<td></td>
</tr>
<tr>
<td>C cell (calcitonin-producing)</td>
<td></td>
</tr>
<tr>
<td>Medullary thyroid cancer</td>
<td>10</td>
</tr>
<tr>
<td>Sporadic</td>
<td></td>
</tr>
<tr>
<td>Familial</td>
<td></td>
</tr>
<tr>
<td>MEN2</td>
<td></td>
</tr>
<tr>
<td>Other malignancies</td>
<td></td>
</tr>
<tr>
<td>Lymphomas</td>
<td>1-2</td>
</tr>
<tr>
<td>Sarcomas</td>
<td></td>
</tr>
<tr>
<td>Metastases</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
</tbody>
</table>
Papillary Cancer

Staging is age dependent ≥ 45

Follicular Cancer
The Good News

In autopsy studies, clinically silent thyroid papillary microcarcinomas (≤ 1 cm) have been reported in up to 36%.

Follow-up studies of patients over 9 years shows no metastases in patients with papillary microcarcinomas < 0.8 cm.
Case 1
HIGH RISK HISTORY

- thyroid cancer in one or more first degree relatives
- history of external beam radiation as a child or exposure to ionizing radiation in childhood or adolescence
- family history of medullary thyroid cancer
- MEN
- hemi-thyroidectomy for previous thyroid cancer
- elevated calcitonin or known RET proto-oncogene mutation
- positive PET scan (routinely not recommended)
Thyroid Nodule - Clinical Differentiation

- Very Suspicious Feature for Thyroid Malignancy
  - Progressive growth
  - Indistinct margins
  - Dyspnea
  - Dysphagia
  - Hard mass
  - Vocal cord paralysis
  - Fixation to skin or surrounding structures
  - Hard, ipsilateral cervical adenopathy
  - History of MEN 2A or 2B
  - Family history of MEN 2A or 2B

(continued)

- Radiation to head or neck
- Evidence of metastases
- Enlargement of nodule during TSH suppression

- Slightly Suspicious Feature for Thyroid Malignancy
  - Male
  - Single nodule
  - Cold nodule
  - Under 20 years of age
  - Very firm mass
A 40 year-old woman presents with a recently discovered painless thyroid nodule. There is no radiation history, no dysphonia or dysphagia.

Examination reveals an easily palpable, firm solitary 2.5 cm thyroid nodule and no cervical lymphadenopathy.

Would you order a thyroid ultrasound?

a. yes, always  89%
b. no, never  5%
c. it depends!  6%
NORMAL THYROID GLAND

- Strap muscles
- Carotid artery

Trachea

Esophagus

Thyroid gland weighs 20 g.

Right/left lobes:
1.5 cm x 1.5 cm x 4 cm.
Isthmus: less than 0.4 cm
Homogenous in echotexture.
ATA Guidelines suggest that thyroid ultrasound should be performed in all patients with one or more suspected thyroid nodules.

Next step?
TSH

- if the TSH is suppressed: Thyroid Uptake and Scan
- if the TSH is normal or elevated: FNA biopsy for most lesions > 1 cm in two dimensions
- if TSH is elevated: Hashimoto’s thyroiditis has slightly higher risk (up to 30%)
Routine use of serum thyroglobulin level is not recommended (lacks sensitivity and specificity)

role of serum calcitonin is controversial - personal or FHx for MEN 2a or 2b
Figure 7. Potential Radionuclide Scan Findings in Individuals with a Thyroid Nodule

Cold

Warm

Hot
“COLD” NODULES NEED FNA BIOPSY
Thyroid Cyst - The “Good”
MIXED - THE “BAD” (POTENTIALLY)

SPONGIFORM
“MIXED”
ULTRASOUND GUIDED FNA

USUALLY A 25 G NEEDLE
ULTRASOUND CLUES TO MALIGNANCY

- solid nodule
- mixed solid and cystic nodule
- hypoechogenicity
- mixed echogenicity
- ill-defined lesion
- central vascularity
- nodule halo absent
- larger vertical than horizontal dimensions
- micro-calcifications
- lymphadenopathy
WHEN TO BIOPSY

<table>
<thead>
<tr>
<th>Condition</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk history: with or without suspicious sonographic features</td>
<td>&gt; 5 mm</td>
</tr>
<tr>
<td>Abnormal cervical nodes</td>
<td>ALL</td>
</tr>
<tr>
<td>Microcalcifications present</td>
<td>≥ 1.0 cm</td>
</tr>
<tr>
<td>Solid nodule: Hypoechoic</td>
<td>&gt; 1.0 cm</td>
</tr>
<tr>
<td>Iso or Hyperechoic</td>
<td>≥ 1.0 - 1.5 cm</td>
</tr>
<tr>
<td>Mixed Cystic and Solid: Suspicious</td>
<td>≥ 1.5 - 2.0 cm</td>
</tr>
<tr>
<td>Not Suspicious</td>
<td>≥ 2.0 cm</td>
</tr>
<tr>
<td>Spongiform</td>
<td>≥ 2.0 cm</td>
</tr>
<tr>
<td>Purely Cystic</td>
<td>FNA Not Indicated</td>
</tr>
</tbody>
</table>
Case 1

A 27 year old man had an MRI to evaluate the effects of head trauma and an asymptomatic neck mass was discovered. He had no predisposing factors to suggest thyroid carcinoma. A 1.8 cm hard nodule was palpable in the left lobe of the thyroid.
THYROID ULTRASOUND

A 1.8 cm mixed solid and cystic nodule, ill-defined medially, hypoechoic lesion with micro-calcifications. There are also a few sub-centimeter cysts scattered throughout.
THE “UGLY”
ABNORMAL LYMPH NODES

- larger vertical than horizontal dimensions
- lack of fatty hilum
- peripheral vascularity
- micro calcifications

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Case 1 (continued)

Cytology suggestive of papillary carcinoma

At surgery, there was metastatic disease involving lymph nodes anterior to the trachea, in the superior mediastinum, and in the anterior cervical triangle
WHAT IS THE ROLE OF MEDICAL THERAPY FOR BENIGN THYROID NODULES?

Benign Thyroid Nodule Treatment Controversy

- TSH suppression doesn’t significantly alter thyroid nodule size
- TSH suppression significantly decreases the size of thyroid nodules
Not recommended: Thyroid hormone in doses that suppress the serum TSH to subnormal levels may result in a decrease in nodule size and may prevent the appearance of new nodules in regions of the world with borderline low iodine intake.

Data in iodine-sufficient populations are less compelling, with large studies suggesting that only about 17–25% of thyroid nodules shrink more than 50%.

J Clin Endocrinol Metab 87:4154–4159.
J Clin Endocrinol Metab 87:4928–4934.
<table>
<thead>
<tr>
<th>GENE/PROTEIN</th>
<th>TYPE OF GENE</th>
<th>CHROMOSOMAL LOCATION</th>
<th>GENETIC ABNORMALITY</th>
<th>TUMOR</th>
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</thead>
<tbody>
<tr>
<td>TSH receptor</td>
<td>GPCR receptor</td>
<td>14q31</td>
<td>Point mutations</td>
<td>Toxic adenoma, differentiated carcinomas</td>
</tr>
<tr>
<td>G&lt;sub&gt;α&lt;/sub&gt;</td>
<td>G protein</td>
<td>20q13.2</td>
<td>Point mutations</td>
<td>Toxic adenoma, differentiated carcinomas</td>
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<tr>
<td>RET/PTC</td>
<td>Receptor tyrosine kinase</td>
<td>10q11.2</td>
<td>Rearrangements PTC1: (inv(10)(q11.2q21)) PTC2: (t(10;17) (q11.2;q23)) PTC3: ELE1/TK</td>
<td>Point mutations PTC</td>
</tr>
<tr>
<td>RET</td>
<td>Receptor tyrosine kinase</td>
<td>10q11.2</td>
<td>Point mutations</td>
<td>MEN 2, medullary thyroid cancer</td>
</tr>
<tr>
<td>BRAF</td>
<td>MEK kinase</td>
<td>7q24</td>
<td>Point mutations, Rearrangements</td>
<td>PTC</td>
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<tr>
<td>TRK</td>
<td>Receptor tyrosine kinase</td>
<td>1q23-24</td>
<td>Rearrangements</td>
<td>Multinodular goiter, papillary thyroid cancer</td>
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<tr>
<td>RAS</td>
<td>Signal transducing p21</td>
<td>Hras 11p15.5 Kras 12p12.1; Nras 1p13.2</td>
<td>Point mutations</td>
<td>Differentiated thyroid carcinoma, adenomas</td>
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<tr>
<td>p53</td>
<td>Tumor suppressor, cell cycle control, apoptosis</td>
<td>17p13</td>
<td>Point mutations, Deletion, insertion</td>
<td>Anaplastic cancer</td>
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<tr>
<td>APC</td>
<td>Tumor suppressor, adenomatous polyposis coli gene</td>
<td>5q21-q22</td>
<td>Point mutations</td>
<td>Anaplastic cancer, also associated with familial polyposis coli</td>
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<tr>
<td>p16 (MTS1, CDKN2A) p21/WAF</td>
<td>Tumor suppressor, cell cycle control</td>
<td>9p21</td>
<td>Deletions</td>
<td>Differentiated carcinomas</td>
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<tr>
<td>MET</td>
<td>Receptor tyrosine kinase</td>
<td>7q31</td>
<td>Overexpression</td>
<td>Follicular thyroid cancer</td>
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<td>c-MYC</td>
<td>Receptor tyrosine kinase</td>
<td>8q24.12-13</td>
<td>Overexpression</td>
<td>Differentiated carcinoma</td>
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<tr>
<td>PTEN</td>
<td>Phosphatase</td>
<td>10q23</td>
<td>Point mutations</td>
<td>PTC in Cowden's syndrome (multiple hamartomas, breast tumors, gastrointestinal polyps, thyroid tumors)</td>
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<tr>
<td>CTNNB1 Loss of heterozygosity (LOH)</td>
<td>β-Catenin Tumor suppressors</td>
<td>3p22 3p; 11q13 Other loci</td>
<td>Point mutations, Deletions</td>
<td>Anaplastic cancer, Differentiated thyroid carcinomas, anaplastic cancer</td>
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<tr>
<td>PAX8-PPARγ1</td>
<td>Transcription factor Nuclear receptor fusion</td>
<td>t(2;3)(q13;p25)</td>
<td>Translocation</td>
<td>Follicular adenoma or carcinoma</td>
</tr>
</tbody>
</table>
INDICATIONS FOR OPERATIVE MANAGEMENT AND REFERRAL

- Lesions > 4 cm - compound, solid or cystic
- Single “cold” lesion
- Recurrent Nodules
- FNA inconclusive / FNA consistent with malignancy
- Inadequate FNA after repeated attempts
- Multiple nodules associated with a history of ionizing radiation
- Nodules increasing in size
- Nodules associated with elevated calcitonin levels
- Symptomatic nodules: airway compression, dysphagia, cosmetic
- High risk patients: male, young, family history
MANAGEMENT OF THYROID NODULES IN PREGNANCY

- evaluate same as for non-pregnant except no radionucleotide scan
- if FNA show DTC, can repeat US at 24 wks - if growth, then surgery / or surgery in 2nd trimester before 24 wks
- for PCT, can keep TSH 0.1 to 1.0
HOW SHOULD THYROID NODULES BE MANAGED IN CHILDREN?

- In some studies, the frequency of malignancy is higher - 15 to 20 %
- FNA is both sensitive and specific
IF BENIGN, WHY FOLLOW

- Multinodular goitre has same risk of malignancy as solitary nodules (one study showed otherwise) J Clin Endocrinol Metab 2006; 91:3411–3417.
- Up to 5% false negative rate with FNA
- Follow-up at 6 to 18 months Ultrasound &/or palpation > 50% increase in volume or 20% increase in 2 dimensions or 20% increase in solid portion

FNA
WHAT CLINICAL FEATURES MIGHT SUGGEST A REFERRAL IS NEEDED?

- rapid growth / steady growth ( > 20% )
- very firm nodule
- fixation to adjacent structures
- nodule > 4 cm
- “cold” on scan
- prior history if head & neck irradiation
- age <20 or > 70 years / male
- paralysis of vocal cords/ dysphagia
- regional lymphadenopathy/ metastases
- Family History of MEN II syndromes
- partially cystic nodule ( “Mixed” )
WHEN TO REFER

❖ “Bad” and “Ugly” - suspicious by history and or ultrasound
❖ confirmed cancer by FNA or Indeterminate pathology - FLUS
❖ Not cysts and not lesions < 0.5cm ⟷ follow
❖ Unsure