Nodular Thyroid Management

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Disclosure
I have no disclosures relevant to this topic

Nodular Thyroid Disease

- Thyroid nodule(s)
  - Solitary or multiple
  - In an otherwise normal gland or a goiter or with underlying autoimmune thyroid disease, Graves’ disease or Hashimoto’s thyroiditis
  - Palpable or non-palpable or incidental
  - Various sizes

**Common Theme - Thyroid Nodule**

Topic Outline

- Pathogenesis
- Epidemiology
- Evaluation
- Ultrasound characterization of thyroid nodules
- Medical management
- Cases
**Risk Factors – Nodular Thyroid Disease**

- Iodine deficiency
  - Hyperplasia -> goiter -> nodular disease
- Smoking
  - Thiocyanate - a competitive inhibitory effect on iodide uptake and organification
- Head and neck irradiation
  - Radionuclear fallouts
  - Total body irradiation for childhood malignancy (Hodgkin’s Lymphoma)
  - From the 1920s to the late 1950s, radiation therapy used for various benign conditions: enlarged thymus glands, tonsils, adenoids, acne, scalp ringworm, impetigo, sinusitis, hemangiomas, and keloids
- Female sex
  - 5-15 times
- Age
- Familial syndromes with increased nodular thyroid disease and thyroid cancer
  - MEN 2, FAP, Gardner’s syndrome, Cowden’s syndrome, Carney complex, Werner syndrome, Pendred syndrome

**Hypothesis for Nodular Transformation**

Schematic diagram of a follicular cell, illustrating the steps involved in thyroid hormone synthesis.

- Protein deficiency
  - Proliferation
  - Mutagenesis
  - Hyperplasia

**Nodular Thyroid Disease**

- Very common
  - In the living population
  - In the dead
Thyroid Nodules - Prevalence

**By palpation**
- Framingham: 4.2% (6.4% women and 1.5% men) 30-60 yo
  - (Vander et al 1968)
- Wickham: 5.3% of women and 0.8% of men, mean age 47
  - (Tunbridge et al 1977)
- **From 100 volunteers in LA: 22%**
  - (Ezzat et al 1994)
  - More patients had TPO antibodies and more female participants

**By ultrasound**
- Non-endemic goiter areas: 19-34%
- In LA: 63% from the study of 100 volunteers

**By Autopsy**
- 50-60%

Malignancy Rate

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Nodule Detection</th>
<th>FNA</th>
<th>Cancer Rate (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 nodule</td>
</tr>
<tr>
<td>USA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCall 1966</td>
<td>442</td>
<td>Scan</td>
<td>Palpation</td>
<td>17</td>
</tr>
<tr>
<td>Sachmechi 2000</td>
<td>443</td>
<td>Scan</td>
<td>palpation</td>
<td>8</td>
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<tr>
<td>Frates 2006</td>
<td>1985</td>
<td>U/S</td>
<td>U/S</td>
<td>15</td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belfiore 1992</td>
<td>5637</td>
<td>Scan</td>
<td>Palpation</td>
<td>5</td>
</tr>
<tr>
<td>Papini 2002</td>
<td>494</td>
<td>U/S</td>
<td>U/S</td>
<td>9</td>
</tr>
<tr>
<td>Deandrea 2002</td>
<td>420</td>
<td>U/S</td>
<td>U/S</td>
<td>6</td>
</tr>
</tbody>
</table>

Modified from Mandel JAMA
Frates et al. JCEM 2006

Malignancy Rate - Autopsy Studies

- 6-11% in most studies
- In U.S.
  - 6.2%, 5 to 10.5mm, 46% multifocal, 14% LN metastasis
  - 1020 autopsies
- In Finland
  - 35.6%, older than 40 yo (43.3% in men and 27.1% in women)
  - 101 consecutive autopsies, with 2-3 mm sections
  - 14%, younger than 40 yo & 27% between 18-40 yo
  - 93 autopsies of children/young adults, with 2-3 mm sections

Lang et al, Am J Clin Pathol 1988
Franssila et al Cancer 1985 and 1986

Thyroid Cancer - Statistics

Nodular Thyroid Disease

- Very common
  - Cancer risk 5-15% with overall low mortality
  - At least 6-11% died without knowing they had thyroid cancer
- Important objectives in the management of nodular thyroid disease
  - To determine which nodules are malignant that require surgery to improve morbidity/mortality
  - To determine functional aberrations that require interventions to improve health

Nodular Thyroid- Evaluation

Which Tests?
- TSH (free T4)
- Anti TPO AB
- Anti Thyroglobulin AB
- TSI or TBII (TRAB)
- Thyroglobulin
- Calcitonin

Which Imaging Studies?
- Ultrasound
- Thyroid scan
- CT
- MRI

Functional Classification of Thyroid Nodule

Thyroid Uptake Scan

- Hot (hyper-functioning)
  - Low malignancy rate – no need to FNA
  - 5-10% of palpable nodules
  - More common in iodine deficient areas
  - At risk for iodine induced thyrotoxicosis
- Cold (nonfunctioning)
  - Most common 50-85% of the nodules
  - Most cancers are cold
  - Most cold nodules are benign - 4.6% cancer*
- Warm (iso-functioning)
  - 10-40%


Nodular Thyroid- Evaluation

- TSH/Free T4
- Anti-TPO AB
  - Consider if TSH elevated (AAE)
- Anti-Thyroglobulin AB
  - Not routinely indicated
  - May consider if elevated TSH and TPO negative (AAE)
- TSI or TBII (TRAB)
  - If hyperthyroid and Graves disease is a differential diagnosis
- Thyroglobulin
  - Not helpful in diagnosing cancer
  - Not routinely recommended in the evaluation of thyroid nodule (ATA, ETA, AAE)
- Calcitonin
  - Routine use controversial
  - ATA: neutral ETA, AAE: consider in MNG
  - We do not routinely measure it except for selected cases
  - Sporadic medullary thyroid cancer rare (0.3-1.3%) of nodular thyroid disease*
  - High rate of false positive results

*Gharib et al Endo Practice 2010 Haugen et al ATA guidelines 2014
Hypercalcitonemia
- Hypercalcemia
- Hypergastrinemia
- Neuroendocrine tumors
- Renal insufficiency
- Chronic autoimmune thyroiditis (controversial)
- Mastocytosis
- Type I pseudohypoparathyroidism
- Heterophile antibodies
- Use of PPI
- Beta-blockers
- Steroids

Risk for MTC based on levels at screening
- A cohort of 5817 patients with thyroid nodules

<table>
<thead>
<tr>
<th>Value pg/mL</th>
<th>PPV for MTC or CCH</th>
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<tbody>
<tr>
<td>&gt;100</td>
<td>100% (MTC)</td>
</tr>
<tr>
<td>50-100</td>
<td>50% (25% MTC and 25% CCH)</td>
</tr>
<tr>
<td>20-50</td>
<td>18.7% (8.3% MTC and 10.5% CCH)</td>
</tr>
<tr>
<td>10-20</td>
<td>1/216 monitored -&gt; 1 had CCH after 2 years of follow up</td>
</tr>
</tbody>
</table>

Ultrasound Evaluation of Thyroid Nodule

**Imaging:**
- No radiation, lower cost
- Better resolution using high resolution ultrasound (sound frequency between 7.5 to 15MHz) than CT
  - Size on u/s correlates with the size at pathology better than CT
- Can detect other nodules in 20-48% of patients with palpable nodules
- Can characterize the nodules
  - To prioritize which nodules to biopsy
- More precise and streamline follow up of thyroid nodules

**Ultrasound Guided Fine Needle Aspiration:**
- Directs FNA to the area of interest
- Shown to improve diagnostic accuracy
  - Lower false negative rate to 0.6%***

*** Danese et al. Thyroid 1998

Prediction of Malignancy by Ultrasound Meta-analysis

<table>
<thead>
<tr>
<th>Features</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR</th>
<th>Diagnostic Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taller than Wide</td>
<td>53</td>
<td>93</td>
<td>5.4</td>
<td>11.14</td>
</tr>
<tr>
<td>Infiltrated Margins</td>
<td>56</td>
<td>85</td>
<td>3.76</td>
<td>6.89</td>
</tr>
<tr>
<td>Internal Calcifications</td>
<td>54</td>
<td>81</td>
<td>3.65</td>
<td>6.78</td>
</tr>
<tr>
<td>Hypo-echogenicity</td>
<td>73</td>
<td>56</td>
<td>1.85</td>
<td>4.5</td>
</tr>
<tr>
<td>Solid</td>
<td>87</td>
<td>56</td>
<td>1.47</td>
<td>4.45</td>
</tr>
</tbody>
</table>

- Intra-nodular blood flow
  - not a good predictor, esp studies with good reference standard
- Nodule size
  - not a predictor
- Combination of features more predictive
  - Infiltrated margins + Internal calcifications

Prediction of Benignity by Ultrasound Meta-analysis

<table>
<thead>
<tr>
<th>Features</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spongiform</td>
<td>10</td>
<td>99</td>
<td>10.1</td>
<td>12</td>
</tr>
<tr>
<td>Cystic</td>
<td>32</td>
<td>98</td>
<td>5.5</td>
<td>6.78</td>
</tr>
<tr>
<td>Iso-echoic</td>
<td>47</td>
<td>84</td>
<td>2.35</td>
<td>3.6</td>
</tr>
<tr>
<td>Increased blood flow</td>
<td>38</td>
<td>86</td>
<td>2.1</td>
<td>3.0</td>
</tr>
</tbody>
</table>
**Papillary Thyroid Cancer**

- Taller than wide
- Hypoechoic with microcalcifications

Sources: Clinic patients & Moon et al. Radiology 247 (3) 2008

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**“Leave Me Alone” Nodules Patterns to Recognize**

- Spongiform nodule – 98.5-99.7% benign
- Pure cystic nodule
- White knight nodule
- Giraffe pattern nodule
- Cystic nodule with clots

Reading et al Ultrasound Quarterly 2005
Bonivita et al AJR 2009

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**Medical Therapy?**

- Levothyroxine suppression not typically recommended
  - Especially in iodine sufficient populations
  - Effects small in areas with sufficient iodine intake
  - Meta-analysis showed lack of significant effects on solitary nontoxic nodule
  - One RCT showed no efficacy in sporadic nontoxic multinodular goiter
  - Potential harms in subclinical hyperthyroidism
  - In areas with low borderline iodine intake - May decrease nodule size and prevent new nodule formation
  - Effects small 5-15% reduction in size
  - Nodules more likely to respond:
    - Small nodule
    - Solid or predominantly solid nodules
    - Abundant colloid on FNA
  - Sufficient iodine intake (150ug) reduced nodule size slightly
  - Avoid excessive intake ie supplements
  - Patients with MNG may become toxic from excessive iodine intake

Castro et al JCEM 2002
Paschke et al. Nat Rev Endocrinol 2011
Haugen et al. ATA guidelines 2014

- Levothyroxine suppression ≠ Levothyroxine replacement
- Treat hypothyroidism
Case 1
• 62 yo presented with a palpable 3-4 cm thyroid mass

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>0.45 - 4.12 mIU/L</td>
<td>&lt;0.03 (L)</td>
<td>0.23 (L)</td>
<td>0.22 (L)</td>
</tr>
<tr>
<td>Free T4</td>
<td>10 - 18 pmol/L</td>
<td>14</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Free T3</td>
<td>385 (145-348)</td>
<td>214 (145-348)</td>
<td>4.4 (2.6-5.7)</td>
<td></td>
</tr>
</tbody>
</table>

Case 1
• US – solitary nodule in the right 4.35 cm. No other nodules
• Uptake scan – toxic nodule
  - No need for biopsy, although it was performed: benign
  - Biopsy suspicions non-hyperfunctioning nodules prior to RAI
• Treated with 35mCi of I131
• Euthyroid TSH 2.2 3 months later and 2.45 8 months later

What to Do?

Case 2
• 41 yo noted a pea sized nodule after a cold
• TSH normal
• FNA benign
• Came to us for a second opinion

Suspicious appearing nodule
- Irregular border
- Hypo-echoic
- microcalcifications

Repeat FNA under U/S
Papillary Thyroid Cancer

Thank You