Case 1

- 28 year old woman sees OB for routine visit
- ROS:
  - Negative except for occasional dysphonia
- PE: BP 122/78, HR 72 BPM, 5’ 5”, 120 lbs.
- Thyroid Exam: 2.5 cm smooth nodule left
  - Moves easily with swallowing
  - 1 cm left SCM lymph node palpable

Goiters and Nodules

- Goiter definition: enlargement of thyroid gland, causes swelling in the neck
  - Endemic goiter; enlargement a response to a lack of iodine
  - Sporadic goiter; hyperplastic or neoplastic overgrowth
    - Toxic nodular goiter; autonomous thyroid hormone production
    - Exophthalmic goiter (Graves’ disease) associated with hyperthyroidism
- Thyroid Nodule: area of different contour or consistency on palpation with differing echotexture on sonographic examination
Thyroid Nodule Prevalence

- By age 30, ~20% of the population has a thyroid nodule (women>men)
- Likelihood of malignancy is higher in the extremes of age (<20 years, >70 years)
- Lifetime likelihood of a nodule is ~60%

Thyroid Cancer - 2014

- 62,980 new cases
- 3x more common in women
  - 47,790 women; 15,190 men
- More lethal in men
  - Deaths: 1060 women, 830 men

Incidence peaks earlier in women (diagnosed in 4th-5th decades) than in men (diagnosed in 6th-7th decades)

Siegel R et al. 2014 CA Cancer J Clin. 64:9-24

Thyroid Cancer Risk: Multinodular (MNG) versus Single Nodule (SN) Goiter

Thyroid Cancer Risk: Multinodular vs. Single Nodule Goiter: Results

- MNGs were associated with a lower risk compared to SN (pooled odds ratio 0.8 [95% CI, 0.67-0.96]; I²=35%)
- A subgroup analysis suggested that this difference depends on the inclusion of studies conducted outside the United States (Outside the US the odds ratio was 0.71 [95% CI, 0.60-0.83]; I²=11%)
- Thyroid cancer may be less frequent in MNG compared to SN, particularly outside the U.S., perhaps due to relative iodine-deficiency in these areas.


Risk Factors for malignancy: Patient History

- Surgical Dx of thyroid cancer in contralateral lobe
- Ionizing Irradiation (XRT) as child/adolescent
- Calcitonin > 100 pg/mL
- PET positive thyroid nodule
- Low dietary iodine intake
- Thyroid cancer in first degree relative

Risk Factors: Family History

- FHx non-medullary thyroid cancer; 1° relative
- Familial adenomatous polyposis (FAP) (> 12%)
- PTEN-hamartoma tumor syndromes
  - Carney complex
  - Werner & Pendred syndrome
- MEN2/FMTC RET proto-oncogene positive
  - Familial medullary thyroid cancer (MTC)
  - Multiple endocrine neoplasia type 2 (MEN 2)
Thyroid Nodule Laboratory Diagnosis

- TSH

WHAT DOES THE TSH LEVEL MEAN?

- Suppressed C/W thyrotoxicosis
  - Malignancy unlikely
  - Elevated C/W hypothyroidism

Haugen BR et al. 2014 ATA Thyroid Nodule and DTC Guidelines
**TSH Concentration & Risk of Malignancy**

<table>
<thead>
<tr>
<th>TSH Concentration</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.4 mIU/L</td>
<td>1</td>
</tr>
<tr>
<td>0.4-0.9 mIU/L</td>
<td>1.31</td>
</tr>
<tr>
<td>1.0-1.7 mIU/L</td>
<td>2.72</td>
</tr>
<tr>
<td>1.8-5.5 mIU/L</td>
<td>3.88</td>
</tr>
<tr>
<td>&gt; 5.5 mIU/L</td>
<td>11.8</td>
</tr>
</tbody>
</table>

*=P<0.05


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**Thyroid Nodule Laboratory Diagnosis**

- **TSH**
  - Suppressed C/W thyrotoxicosis
    - Malignancy unlikely
  - Elevated C/W hypothyroidism

**RADIONUCLIDE SCANNING**

*Indication:*
- Thyrotoxic nodule identification (TSH < normal)
- 99mTc (False +s), 131-I (Rads) or 123-I (Std)

Haugen BR et al. 2014 ATA Thyroid Nodule and DTC Guidelines

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**Thyroid Ultrasound**

*Indication: normal to ↑ TSH*
- Defines a distinct nodule vs. abnormal parenchyma
- Role to guide FNA (cystic, posterior)
- MNG nodule selection
- Useful in f/u of low risk patient, incidentaloma

**MRI / CT SCANNING**

- Offer little in pre-operative diagnosis
- Contrast administration may delay Dx &/or Rx

Haugen BR et al. 2014 ATA Thyroid Nodule and DTC Guidelines
Analysis of US Predictors

- **Characteristic** | **Sensitivity** | **Specificity**
- Microcalcification | 44% | 89%
- Hypoechoic | 81% | 53%
- Solid | 86% | 18%
- Absence of Halo | 66% | 54%
- Intranodal vascularity | 62% | 77%
- Poorly defined margin | 55% | 79%
- Taller than Wide | 48% | 92%

Haugen BR et al. 2014 ATA Thyroid Nodule and DTC Guidelines

Papillary Thyroid Cancer Appearance on U/S

- 58 male, 10 mm mass + microcalcifications
- 39 female, 9 mm mass + irregular margins

Tae et al. Thyroid 2007 17:461-466

Ultrasound Pattern = Risk

- **High Suspicion** = 70-90% Cancer Risk
  - Hypoechoic, microcalc., irregular border
  - Hypoechoic, microlobulated margin
  - Hypoechoic, irreg margin, Taller than wide
  - Hypoechoic, irreg margin, X-thyroid Extension
  - Irregular margins, suspicious Lymph nodes

- **Intermediate suspicion** = 10-20% Risk
  - Hypoechoic with regular margins

Haugen BR et al. 2014 ATA Thyroid Nodule and DTC Guidelines
Ultrasound Pattern = Risk

- **Low Suspicion** = 5-10% Risk of cancer
  - Hyperechoic, solid, regular margins
  - Isoechoic, solid, regular margins
  - Partially cystic, eccentric solid area

- **Very Low suspicion** = <3% Risk of cancer
  - Spongiform, partially cystic no suspicions features

- **Benign**
  - Purely cystic

Haugen BR et al. 2014 ATA Thyroid Nodule and DTC Guidelines

Who to Biopsy? R8

Modify Size cutoffs by:
- Patient risk factors
  1. FHx Thy Ca (1°), Hx XRT/Ion Irrad (child),
  2. Surg Dx Thy Ca, PET pos nodule, RET pos.,
  3. Calcitonin > 100 pg/ml, MEN, FMTC
- Presence of Sonographically Suspicious LNs
- US FNA of Sono Suspicious LNs

Haugen BR et al. 2014 ATA Thyroid Nodule and DTC Guidelines

Multiple Nodules R20

- When multiple nodules ≥ 1 cm are present, FNA based upon US pattern
  - Strong Recommendation, Mod Qual evidence
- If multiple sonographically similar low or very low risk nodules are present, malignancy risk is low, reasonable to FNA largest (1.5-2.0 cm) and observe others.
  - Weak Recommendation, Low Qual evidence

Haugen BR et al. 2014 ATA Thyroid Nodule and DTC Guidelines
### Malignancy Prediction: Bethesda System

<table>
<thead>
<tr>
<th>Category</th>
<th>Malignant risk</th>
<th>What next?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Diagnostic</td>
<td>1-4%</td>
<td>Re-do (U/S)</td>
</tr>
<tr>
<td>Benign</td>
<td>0-3%</td>
<td>Clinical F/U</td>
</tr>
<tr>
<td>Atypical</td>
<td>5-15%</td>
<td>Re-do (U/S)</td>
</tr>
<tr>
<td>Follicular Neoplasm</td>
<td>15-30%</td>
<td>Lobectomy</td>
</tr>
<tr>
<td>Suspect malignancy</td>
<td>60-75%</td>
<td>Total Tx</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99%</td>
<td>Total Tx</td>
</tr>
</tbody>
</table>

*FNA = fine needle aspiration


### Indeterminate: What Next?

- Mutation Panel
  - BRAF, RET, RAS, RET/PTC, PAX8/PPARγ
  - High Positive Predictive value (80-90%)
- Multigene classifier: identify benign nodule
  - High Negative predictive value (94-95%)
- TSH Receptor mRNA in circulation
  - High Positive Predictive value (96%)

### FNA Disposition

- Inadequate: Repeat FNA US guidance
- Inadequate: Close F/U Surgery?
- Malignant: Surgery
- Indeterminate: Repeat FNA Cytogenetics?
- Indeterminate: Mutation
  - Mut. Neg.
  - Mut. Pos.
  - B9
- Benign: Follow
- T-Tx
- Hemi Tx
- Surgery