Thyroid Nodule T/F Pre-Test

1. Thyroid Nodules are uncommon in the elderly.
2. The history accurately diagnoses benign nodules.
3. Elevated TSH predicts a benign nodule.
4. A Multi Nodular Goiter does not harbor cancer.
5. “Hot” thyroid nodules may be treated with 131-I.
6. Incidentalomas less than 1 cm are benign.
7. 90% of indeterminate nodules are malignant.
8. Cytogenetic testing has no role in clinical decisions.
9. Papillary thyroid cancer does not cause mortality.

PRACTICE GUIDELINES:
Thyroid Nodules and Cancer 2013

James V. Hennessey MD
Associate Professor of Medicine
Harvard Medical School

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
Questions to be answered:

- How frequently are thyroid nodules and thyroid cancer encountered?

THYROID NODULES

- PREVALENCE:
  - 30-50% Risk of nodule (U/S or Autopsy)
  - 4-8% risk palpable nodule
- THYROID CANCER
  - 60,220 cases in U.S. 2013 (Estimate)
  - 0.005% of U.S. population
  - < 5% fatal (1850 deaths in 2013 estimated)

Siegel R et al. CA Cancer Journal for Clinicians 2012 62:10-29
Questions to be answered:

- What is the likelihood that a nodule once identified is malignant?
- How would one differentiate benign from malignant nodules?
- How about with simple vital signs?

Obesity Impact on Thyroid Cancer

- 16,481 subjects (8,741 Men)
  - Free of personal and FHx of thyroid disease
- Underwent screening U/S 2007/2008
  - Thyroid cancer by Surgical Dx in 227 (1.4%)
- Association of BMI and incidence of thyroid cancer in women in MVA
  - OR = 1.63 (1.2-2.18 p=0.001) / 5 kg/m2

Han J et al. 2012 ATA Poster 84

DIAGNOSIS:
Hx favors benign diagnosis?

- FHx Hashimoto’s
  - Probably NOT
- FHx of MNG
  - Probably NOT
- FHx Benign nodule
  - NOT helpful
- Sx of Hyperthyroidism

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THYROID NODULE Dx

<table>
<thead>
<tr>
<th>TSH&gt;0.4</th>
<th>TSH&lt;0.4</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant Dx</td>
<td>4.8%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

KUMAR, FRANKLYN ET AL. 1999 THYROID 9:1105-1109

TSH & Risk of Malignancy

Adjusted Odds Ratio

Boelaert et al. 2006 JCEM 91(110:4295-301

TSH and Malignancy Risk

843 Surgical patients with pre-op TSH

Haymart MR et al. 2008 JCEM 93:809-14

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**DIAGNOSIS:**

Hx favors *benign* diagnosis??

- Nodule soft, smooth, mobile
  - Perhaps BUT not reliable
- Sx of Hypothyroidism or pain
  - Hypothyroidism may actually increase the likelihood of malignancy
  - Cancers may also bleed
- MNG (No dominant nodule)???
**DIAGNOSIS: Hx favors Malignant diagnosis**

- **AGE:** Young (<20), Old (>70)
  - Likely hood of malignancy higher in the extremes of age
- **Males >> Women**
  - And the data shows:

**THYROID NODULE Dx**

<table>
<thead>
<tr>
<th>Malignant Diagnosis</th>
<th>Male</th>
<th>Female</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KUMAR, FRANKLYN ET AL. 1999 THYROID 9:1105-1109</td>
<td>10.4%</td>
<td>4.5%</td>
<td>0.007</td>
</tr>
<tr>
<td>Frates MC and Larsen PR et al. 2006 JCEM 91:3411-17</td>
<td>20.2%</td>
<td>14.1%</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Lu Z et al. 2011 W J Surg 35:122-127</td>
<td>17.1%</td>
<td>11.5%</td>
<td>NR</td>
</tr>
</tbody>
</table>
DIAGNOSIS: Hx favors Malignant diagnosis

History of Radiation exposure
- (Chernobyl 04/26/1986 and ≤ 14 years)
- Little impact on 99 highly exposed workers (>21 years)
- Symptoms of dysphagia, hoarseness
- Nodule is firm, hard, irregular or fixed
- Presence of cervical lymph nodes
- Family history of thyroid cancer
  - MCT and Papillary thyroid cancers familial

Summary of High Risk History
1. Family Hx Thyroid Cancer 1st relative
2. Hx XRT/Ionizing Irradiation as child (Adolescent)
3. Surgical Dx Thyroid Cancer in contralateral lobe
4. 18FDG-PET positive nodule
5. MEN2/FMTC RET proto-oncogene positive
6. Calcitonin > 100 pg/ml
7. MEN 2 (MCT, Hyperpara., Pheochromocytoma
8. Familial Medullary Thyroid Cancer
  - Cooper DS et al. 2009 Thyroid 19:1167-1214

Case 2
- 72 year old man presents with palpitations
- ROS: 14 lb weight loss over last 6 months
- PE: BP 152/84, PR 112 irregular
  - Eyes: alert stare present?
  - Thyroid: 3.5 cm left nodule freely movable
  - Cor: Irregularly irregular rhythm, no M/G/R
  - Lungs: bibasilar rales
  - LE: 1+ edema
LABORATORY DIAGNOSIS

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

- **FT4**
  - Indicated for abnormal TSH

- **FT3**
  - Indicated for suppressed TSH

*Cooper DS et al. 2009 Thyroid 19:1167-1214*

LABORATORY DIAGNOSIS

- Impact of PE on TFTs
  - 50 consecutive patients undergoing thyroid PE
    - Gr 1 TNC patients
    - Gr 2 NIUS (no nodule)
  - TFTs drawn before and 2 hours AFTER Thyroid examination
  - TT4 and TSH NO ∆!!

*Toros SZ et al. 2010 laryngoscope 120(7):1322-5*

RADIONUCLIDE SCANNING

- **Indication:**
  - Thyrotoxic nodule ID (TSH < normal) (A) *

- **99mTc**
  - Rapid, inexpensive, 10% “Hot” nodule false +

- **131-I**
  - Inexpensive, relative ↑ radiation exposure

- **123-I**
  - Expensive, least radiation exposure, standard

*Cooper DS et al. 2009 Thyroid 19:1167-1214*
“HOT” NODULE

Radioiodine 123 Scans of Hyperfunctioning Thyroid Nodules With and Without Suppression of Extranodular Thyroid


“HOT” NODULES THERAPY

- Autonomous “Hot” Nodule
  - “For practical purposes, autonomous thyroid nodules are not malignant” (rare exceptions)
- Indication:
  - Large Nodules (>2.5 cm ø)
  - Thyrotoxic patients
- Treatment:
  - 131-I
  - Surgery
Further Laboratory Dx (nl / ↑ TSH)

- Anti-TPO
  - Indicated for elevated TSH
  - Positive C/W presence of Hashimoto’s
- Thyroglobulin (F) R 3
  - Primarily useful in post operative follow up
- Thyrocalcitonin (> 100 pg/ml MCT likely)
  - Not routinely recommended in USA (I) R 4

Cooper DS et al. 2009 Thyroid 19:1167-1214

RADIOLOGIC DIAGNOSIS

- THYROID ULTRASOUND (A) R 2
  - Now routine recommended (nl to ↑ TSH)
  - Define the presence of a nodule vs. abnormal parenchyma
  - Role to guide FNA (cystic, posterior) (B)
  - MNG nodule selection
  - Useful in fu of low risk patient, incidentaloma
- MRI / CT SCANNING
  - Offer little in pre-op diagnosis
  - Contrast administration may delay Dx &/or Rx

Cooper DS et al. 2009 Thyroid 19:1167-1214

Case 3

- 63 year old woman seen in the ER for dizziness.
- PE: Stable VS, Thyroid “nl”, Heart RRR
- Labs: Routine chemistry “nl”, TSH 2.3 IU/L
- Carotid Ultrasound: No vascular lesion
  - Three 0.8-1.1 cm hypoechoic nodules left thyroid lobe
    - Ultrasoundographic features described
    - Doppler flow study performed

Data
Incidentaloma Facts

- **Frequency:** 19-67% in prospective studies
- Thyroid **Cancer** found in 4% of FNAs
  - ↑ the # of nodule FNAs will → ↑ Cancer rates
- Incidental thyroid cancer characteristics:
  - Capsule **invasion** 20% or Extra thyroidal 17-21%
  - Positive cervical lymph **nodes** 12-25%
  - Tumor **multifocality** 32-39%
  - Distant **metastases** 1.6-2.5%
  - Thyroid cancer specific **mortality** 1%

Mazzaferri, E. 2006 JAMA 295:2179-2182

US Features: Thyroid Nodules

- **Discrete,** distinguished from parenchyma
- **High Risk Features:** **Size** - Not predictive of malignancy
  - **Taller than wide** on transverse view
  - Echogenicity- **Hypoechocic** more likely malignant
  - Composition- Solid (<25% cystic) vs. Cystic (>75%)
  - Calcification- **Micocalcifications** (Psammoma bodies)
  - Halo- Absence more likely malignant
  - Margins- Irregular, **infiltrative**
  - Internal blood flow- **increased vascularity**

Cooper DS et al. 2009 Thyroid 19:1167-1214

No Size/ Malignancy link?

P < .01

Kamran SC et al. 2013 98(2):564-70.
Thyroid Appearance on U/S

Mandel SJ: 2004 JAMA 292:2632-42

R lobe
L lobe

Carotid

Solid Nodule R lobe

Asymmetric L lobe
(no nodule)

Papillary Thyroid Cancer Appearance on U/S

Tae et al. Thyroid 2007 17:461-466

58 male, 10 mm mass + microcalcifications

39 female, 9 mm mass + irregular margins

Who should be biopsied?

<table>
<thead>
<tr>
<th>Feature</th>
<th>Size Threshold</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid Nodule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AND hypoechoic</td>
<td>&gt; 1 cm</td>
<td>B</td>
</tr>
<tr>
<td>AND iso- or hyperechoic</td>
<td>≥ 1-1.5 cm</td>
<td>C</td>
</tr>
<tr>
<td>Mixed cystic-solid nodule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WITH suspicious feature</td>
<td>≥ 1.5-2.0 cm</td>
<td>B</td>
</tr>
<tr>
<td>W-OUT suspicious feature</td>
<td>≥ 2.0 cm</td>
<td>C</td>
</tr>
<tr>
<td>Spongiform nodule</td>
<td>≥ 2.0 cm</td>
<td>C</td>
</tr>
<tr>
<td>Purely Cystic nodule</td>
<td>Not indicated</td>
<td>E</td>
</tr>
</tbody>
</table>

Cooper DS et al. 2009 Thyroid 19:1187-1214
Who should be biopsied?

<table>
<thead>
<tr>
<th>Feature</th>
<th>Size Threshold</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-Risk History*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With suspicious feature</td>
<td>&gt; 5 mm</td>
<td>A</td>
</tr>
<tr>
<td>W-out suspicious feature</td>
<td>&gt; 5 mm</td>
<td>I</td>
</tr>
<tr>
<td>Abnormal Cervical LN</td>
<td>All</td>
<td>A</td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>≥ 1 cm</td>
<td>B</td>
</tr>
</tbody>
</table>

* FHx Thy Ca (1°), Hx XRT/Ion Irrad (child), Surg Dx Thy Ca, PET pos nodule, RET pos., Calcitonin > 100 pg/ml, MREN, FMTC

Cooper DS et al. 2009 Thyroid 19:1167-1214

FINE NEEDLE ASPIRATION

- Most effective method of D/D (A) R 5
- **Indication:**
  - Normal → elevated TSH
  - All possibly malignant nodules
  - When patient surgical candidate
- **Sensitivity** 68-98%
- **Specificity** 72-100%

Cooper DS et al. 2009 Thyroid 19:1167-1214

FNA FINDINGS: DIAGNOSIS

- Benign diagnosis 75%
  - Benign nodule, Hashimoto’s Thyroiditis
- Suspicious or inadequate 20%
- Non-diagnostic 15-20% in good centers
  - Cancer rates 5-9% at surgery
- Follicular Neoplasm
  - 30-60% malignant Pathology
  - Malignancies (Papillary, Follicular, Hurthle cell)
FNA Malignancy Prediction with Bethesda System

- Category | Risk of Malig | What next?
- Non-Dx 1-4% | Re-do (U/S)
- Benign 0-3% | Clinical F/U
- Atypical 5/15% | Re-do (U/S)
- Folli Neoplas. 15-30% | Lobectomy
- Suspicious 60-75% | Total Tx
- Malignant 97-99% | Total Tx

Indeterminate: What Next?

- Mutation Panel
  - BRF, 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%)

Malignant Diagnoses

- Papillary Carcinoma
  - 75-85% of new cases diagnosed
- Follicular Carcinoma
  - 10-20%
  - FNA: C/W Follicular Neoplasm
- Hürthle cell lesions
  - Adenomas and Carcinomas
- Medullary Thyroid Cancer
  - 3-5%
- Anaplastic Thyroid Cancer
  - 1-2%

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Relative Survival by Histology of Thyroid Carcinomas Diagnosed Between 1985-1990a

Hundahl SA et al. 1998 Cancer 83:2053-48

Nodule Work-up

Referral

Cooper et al. 2006 Thyroid 16 (2):1-33
FNA Disposition

- Inadequate
  - Repeat FNA
  - US guidance

- Malignant
  - Surgery

- Indeterminate
  - Repeat FNA
  - Cytogenetics?

- Benign
  - Follow

- Close FNA
  - Surgery

- Mutation
  - Mutation
  - Mut. Neg.

- Surgery T-Tx
  - Surgery Hemi T

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