Thyroid Nodules

UCSF Internal Medicine Updates
May 22, 2017
Elizabeth Murphy, MD, DPhil

No conflicts

Overview

- Thyroid nodule and cancer review
- Ultrasound
- FNA cytology
- Nodule follow up
- Putting it all together
52 yow comes to clinic complaining of fatigue and cold intolerance. TSH 20, Repeat TSH 22
FT4 low
Exam: Thyroid is slightly firm, no discrete nodules, perhaps slightly enlarged

What to do next?
  a) Treat with levothyroxine
  b) Treat and check a TPO antibody
  c) Treat and check an ultrasound
  d) Treat, check TPO and check an ultrasound

52 yow comes to clinic complaining weight loss and palpitations. TSH <0.01 Repeat TSH <0.01
FT4 high
Exam: no proptosis, thyroid is enlarged 2-3X, no discrete nodules, non-tender

What to do next?
  a) Treat hyperthyroidism
  b) Treat and check TSH receptor antibody
  c) Treat and check an ultrasound
  d) Treat, check TRAB and check an ultrasound

THYROID NODULES

50% adults with a nodule on ultrasound

7% adults with a palpable nodule
Some Thyroid Nodule Facts

- Benign to malignant nodules
  - Some data 2% cancer 98% benign
  - Other data suggests 5-10% cancer (rates with bias)
- Prior to FNA 14% of resected nodules were malignant
- Now (2007) 56% of nodules resected are malignant

1Yassa et al, Cancer 111:508 2007

Thyroid Cancer

- 1% of all cancer
- 0.5% of cancer deaths
- 20 year cancer specific survival is 97% even without treatment


Types of Thyroid Cancer

- Differentiated Thyroid Cancer
  - Papillary
  - Follicular
  - Hurthle Cell
- Medullary Thyroid Cancer (c-cells, MEN2, RET mutation, calcitonin)
- Anaplastic Thyroid Cancer
- Lymphoma, metastasis, other
Papillary Thyroid Cancer Variants

- Microcarcinoma (< 1 cm) - 33% (all types)
- Classical Variant - 32%
- Tall Cell Variant - 7%
- Follicular Variant 37%
  - Infiltrative
  - Encapsulated with invasion
  - Encapsulated without invasion

Follicular Variant of Papillary Cancer

- Difficult to accurately diagnose on FNA
- Subtypes
  - Infiltrative
  - Encapsulated with invasion
  - Encapsulated without invasion
Follicular Variant of Papillary Cancer

- Difficult to accurately diagnose on FNA
- Subtypes
  - Infiltrative 6%
  - Encapsulated with invasion 4%
  - Encapsulated without invasion 17%

NIFTP
(Non-Invasive Follicular Thyroid neoplasm with Papillary-like nuclear features)

- Follicular Variant of Papillary Thyroid Cancer
  - Encapsulated
  - No invasion
- Clonal origin with molecular alterations distinct from PTC
- Indolent course, recurrence < 1% over 15 years

Nikiforov et al, JAMA Oncology, 2016, 2:1023.

Thyroid-Cancer Incidence and Related Mortality in South Korea, 1993–2011.

Thyroid Cancer in the US

Penetration of Thyroid-Cancer Screening (2008–2009) and Incidence of Thyroid Cancer (2009) in the 16 Administrative Regions of South Korea.

Observed versus Expected Changes in Age-Specific Incidence of Thyroid Cancer per 100,000 Women, 1988–2007.
Observed versus Expected Changes in Age-Specific Incidence of Thyroid Cancer per 100,000 Women, 1988–2007.

United States Increase in Thyroid Cancer from 1988-2002
- 49% from Papillary Thyroid Cancer < 1 cm
- 87% from Papillary Thyroid Cancer < 2 cm
- High median income zip code is a risk factor
- 75% of cases in women and 49% in men represent overdiagnosis


Thyroid Cancer in the US

Case

52 year old woman found on cervical spine MRI to have an incidental 1.5 cm thyroid nodule. No known h/o thyroid disease and otherwise healthy. No meds. Non-smoker, no history of radiation exposure. Family history negative. Nodule not palpable and no cervical LAN.

What labs next?

a) TSH
b) TSH and Free T4
c) TSH +/- Free T4 plus TGB and/or TPO antibody
d) Any combination of above with a thyroglobulin or calcitonin
Case

52 year old woman found on cervical spine MRI to have an incidental 1.5 cm thyroid nodule. No known h/o thyroid disease and otherwise healthy. No meds. Non-smoker, no history of radiation exposure. Family history negative. Nodule not palpable and no cervical LAN.

TSH is normal, what next?

a) Leave it alone
b) Send for FNA
c) Send for US without FNA so you can decide later
d) Send for US guided FNA
e) Send for US and I-123 nuclear medicine scan
Who does your Ultrasounds?

a) I have an endocrinologist I send patients to and she does both US and FNA
b) Radiologist(s) that specialize in US
c) Radiology practice with multiple providers who I really trust
d) Radiology practice with multiple providers that I’m not always confident of their reports

How do you decide what to FNA?

a) Send to an endocrinologist to decide.
b) FNA based on the recommendation of the radiologist.
c) Decide almost entirely based on the details of the radiology report rather than the radiologists specific recommendation.
d) A combination of b and c.

Thyroid Cancer Risk Factors
In Folks with a Thyroid Nodule

• Age (< 20 or > 70)
• Male - Odds Ratio 2¹
• Family history
• > 4 cm?
• Rapidly growing (as long as it’s not a cyst)
• History of radiation exposure
  — Childhood cancer survivor
• PET positive (incidental finding)
• Higher TSH

Worrisome Features on Ultrasound

- Microcalcifications
- Hypoechoic
- Solid
- Abnormal lymph nodes
- Extrathyroidal extension
- Large
- Central Vascularity
- Irregular Margins
- Tall > Wide
- Coarse calcifications
- Absence of Halo

Screening Test
1. A simple test performed on a large number of people to identify those who have or are likely to develop a specified disease.
2. Diagnostic performance and efficacy
   - Sensitivity, specificity, PPV, NPV, ROC, LR
3. Discovery of disease should be actionable (Treatment efficacy)
   - Proportion of cases helps planning treatment
   - Proportion where treatment is changed after test
4. Patient outcomes (benefit should outweigh harm)
   - Proportion of tested patients who improve versus untested
   - Decrease in incidence of morbidities in tested versus untested
5. Cost Effectiveness
Bias in Nodule Studies

Ascertainment Bias: Outcomes are often obtained only in patients with suspected abnormalities. You don’t learn about misses and true rates of disease.

Over diagnosis Bias: If you look for disease, you will find a large reservoir of cases that would never have been symptomatic, and that you otherwise would never have known about. Increased morbidity without improved outcome?

Selection Bias: Group selected to study is not a representative group of patients.

Accuracy Statistics

- **Sensitivity** tells you about how well the test performs in patients with the disease you are looking for
- **Specificity** tells you about how the test performs in normals
- **PPV** – Probability that positive screen represents disease. Very sensitive to disease prevalence.
- **NPV** – Probability that subjects with negative result don’t have the disease.
- **Likelihood ratio** – Uses the sensitivity and specificity of the test to determine whether a test result usefully changes the probability that a condition (such as a disease state) exists. How well does the test discriminate between those affected and those not

Accuracy of Ultrasound

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcalcifications</td>
<td>44</td>
<td>89</td>
</tr>
<tr>
<td>Hypoechoic</td>
<td>81</td>
<td>53</td>
</tr>
<tr>
<td>Solid</td>
<td>86</td>
<td>18</td>
</tr>
<tr>
<td>Absence of Halo</td>
<td>66</td>
<td>54</td>
</tr>
<tr>
<td>Vascularity</td>
<td>62</td>
<td>77</td>
</tr>
<tr>
<td>Irregular Margins</td>
<td>55</td>
<td>79</td>
</tr>
<tr>
<td>Tall &gt; Wide</td>
<td>48</td>
<td>92</td>
</tr>
<tr>
<td>Feature</td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>-------------------------</td>
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- Other studies with “substantial” interobserver agreement (> 60%)

*Cheng et al., Head and Neck, 2013.

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**Thyroid US Guidelines**

- Society of Radiologists in Ultrasound
- American Thyroid Association
- American Association of Clinical Endocrinologists
- European Thyroid Association
- Associazione Medici Endocrinologi
- Korean Society of Neuro and Head and Neck Radiology

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**Problems with US Studies**

- Most studies are limited to FNA’d nodules
- Nodules without worrisome features are not studied (so don’t know how many you missed)
- Makes US look better than it is
Accuracy of Thyroid US FNA Guidelines

<table>
<thead>
<tr>
<th></th>
<th>SRU</th>
<th>NCCN</th>
<th>ATA</th>
<th>TIRADS French</th>
<th>Kim</th>
<th>TIRADS Kwak</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>54</td>
<td>93</td>
<td>96</td>
<td>95</td>
<td>87</td>
<td>99</td>
</tr>
<tr>
<td>Specificity</td>
<td>75</td>
<td>40</td>
<td>41</td>
<td>52</td>
<td>83</td>
<td>26</td>
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<tr>
<td>PPV</td>
<td>38</td>
<td>31</td>
<td>32</td>
<td>36</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>NPV</td>
<td>85</td>
<td>95</td>
<td>97</td>
<td>97</td>
<td>90</td>
<td>99</td>
</tr>
</tbody>
</table>

Which guideline does your radiologist follow?

ATA nodule sonographic patterns and risk of malignancy

Yoon et al, Radiology, 2017, epub ahead of print
Pure cyst – No FNA

<1 % malignancy
No biopsy (except to drain)

Spongiform Nodule – No FNA

• More than 50% of nodule contains microcystic areas


High Suspicion

• Hypoechoic solid nodule or solid component of partially cystic nodule with one or more of:
  – Irregular margins (infiltrative/microlobulated)
  – Microcalcifications
  – Taller than wide
  – Rim calcifications with small extrusive soft tissue component
  – Evidence of extrathyroidal extension

• FNA \geq 1 \text{ cm}
• ATA estimated malignancy risk \geq 70-90%
• Strong recommendation, moderate quality data
Follow up on all US Patients

- Retrospective study of 11,618 patients at UCSF over 5 years (FNA and not FNA)
- Mean f/u 3.7 years, minimum 2 years
- Linked to California Cancer Registry outcomes

Patients
- thyroid cancer patients (n=105)
- Age, gender matched control cohort followed for at least 2 years (n=369)


Table 1: Histologic Findings of the Study Cancers

<table>
<thead>
<tr>
<th>Type of Thyroid Cancer</th>
<th>Cancers, No. (%)</th>
<th>Size, Mean (Range), cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>85 (81.0)</td>
<td>1.7 (1.0-7.6)</td>
</tr>
<tr>
<td>Follicular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimally Invasive</td>
<td>6 (5.7)</td>
<td>3.8 (1.7-8.5)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>1 (1.0)</td>
<td>3.0*</td>
</tr>
<tr>
<td>Not otherwise specified</td>
<td>3 (2.8)</td>
<td>2.6 (1.3-5.8)</td>
</tr>
<tr>
<td>Medullary</td>
<td>6 (5.7)</td>
<td>2.6 (1.6-3.8)</td>
</tr>
<tr>
<td>Papillary</td>
<td>1 (1.0)</td>
<td>Extensive§</td>
</tr>
<tr>
<td>Not specified</td>
<td>2 (2.8)</td>
<td>NA</td>
</tr>
</tbody>
</table>


Multivariate Results:
Variables Significantly Associated with Thyroid Cancer

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro-calcifications</td>
<td>8.5</td>
</tr>
<tr>
<td>Nodule size &gt; 2cm</td>
<td>2.8</td>
</tr>
<tr>
<td>Solid composition</td>
<td>2.1</td>
</tr>
</tbody>
</table>

High Suspicion

- **Hypoechoic solid nodule** or solid component of partially cystic nodule with one or more of:
  - Irregular margins (infiltrative/microlobulated)
  - Microcalcifications
  - Taller than wide
  - Rim calcifications with small extrusive soft tissue component
  - Evidence of extrathyroidal extension
- FNA ≥ 1 cm
- ATA estimated malignancy risk >70-90%
- Strong recommendation, moderate quality data

What to look for in an Ultrasound Report

- First jump to the details of the report.
- Scan for:
  - Size of the nodules
  - Does it discuss of presence or absence of microcalcifications or vascularity
  - Is it solid
  - Does the report note assessment of lymph nodes
- See if recommendation for FNA comes with mention of the guideline on which it is based.

What about those other Risk Factors?
TSH associated with higher odds of Thyroid Cancer

- Present at normal and even subnormal TSH levels
- Doubling of thyroid cancer risk within the normal TSH range from 0.65 to 4
- Doubling of thyroid cancer risk with TSH from 2.2 to 7
- May also be associated with prognosis (more aggressive thyroid cancer, more nodal mets)
What are Endocrinologists doing?
Thyroid Pathology

The Bethesda System - 2008

- Non-Diagnostic or Unsatisfactory
- Benign
- AUS/FLUS (Atypia of Undetermined Significance, Follicular Lesion of Undetermined Significance)
- Follicular neoplasm/Suspicious for Follicular Neoplasm
- Suspicious for malignancy
- Malignant
Nondiagnostic or Unsatisfactory

1-4% Malignancy Risk
2-20% of FNA (goal < 10%)

• Cyst fluid only (often with macrophages, should be reported as such)
• Obscuring blood, clot artifact, drying artifact etc.

Benign

0-3% Malignancy Risk
60-70% of FNA

• Consistent with a benign follicular nodule (adenomatoid nodule, colloid nodule etc)
• Consistent with lymphocytic (Hashimoto) thyroiditis
• Consistent with granulomatous (subacute) thyroiditis
• Other

AUS/FLUS

< 20% Malignancy risk?
3-6% of FNA

• Controversial category created by vote
• “The heterogeneity of this category precludes outlining all scenarios for which an AUS interpretation is appropriate”
• If rates > 7% have a talk with your pathologist

POSSIBLE PLANS:
  – Follow clinically
  – Repeat FNA with or without molecular testing
  – Lobectomy
Follicular Neoplasm
(or suspicious for follicular neoplasm)
15-30% Malignant

- At lobectomy can find:
  - Follicular adenoma
  - (Hurthle cell adenoma)
  - Adenomatoid nodules of a multinodular goiter
  - Follicular carcinoma
  - (Hurthle cell carcinoma)
  - Follicular variant of papillary carcinoma

Suspicious for Malignancy
60-75% Malignant

- Suspicious for papillary carcinoma (often follicular variant)
- Suspicious for medullary carcinoma
- Suspicious for metastatic carcinoma
- Suspicious for lymphoma
- Other

Malignant
97-99% Malignancy Risk
3-7% of FNA
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Risk of Malignancy (Bethesda estimate)</th>
<th>Risk of Malignancy in Tumors taken out</th>
<th>Relative Proportion of FNA Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diagnostic</td>
<td>1-4%</td>
<td>20%</td>
<td>2-20% (&lt;10% goal)</td>
</tr>
<tr>
<td>Benign</td>
<td>0-3%</td>
<td>2.5%</td>
<td>60-70%</td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>&lt;20%</td>
<td>14%</td>
<td>2-29% (&lt;7% goal)</td>
</tr>
<tr>
<td>FN/SFN</td>
<td>15-30%</td>
<td>25%</td>
<td>10%?</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>60-75%</td>
<td>70%</td>
<td>10%?</td>
</tr>
</tbody>
</table>

**Interobserver Diagnostic Agreement**

- 25% concordant diagnoses (15 samples)
- 53% two diagnoses (32 samples)
- 18% three diagnoses (11 samples)
- 3% four diagnoses (2 samples)


**Thyroid Pathology**

*The Bethesda System*

- Non-Diagnostic or Unsatisfactory
- Benign
- AUS/FLUS – 42 discordances
- FN/SFN
- Suspicious for malignancy
- Malignant
Thyroid Pathology
The Bethesda System

- Non-Diagnostic or Unsatisfactory
- Benign
  - AUS/FLUS – 42 discordances
  - FN/SFN – 25 discordances
  - Suspicious for malignancy
- Malignant

- Non-Diagnostic or Unsatisfactory – 7 discord.
- Benign
  - AUS/FLUS – 42 discordances
  - FN/SFN – 25 discordances
  - Suspicious for malignancy – 31 discordances
- Malignant
Intraobserver Diagnostic Agreement

<table>
<thead>
<tr>
<th>Cytopathologist</th>
<th>TBS/F scheme (six categories)</th>
<th>Proposed simplified scheme (four categories)</th>
<th>No. of cases re-reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100%</td>
<td>100%</td>
<td>12</td>
</tr>
<tr>
<td>B</td>
<td>75%</td>
<td>83%</td>
<td>8</td>
</tr>
<tr>
<td>C</td>
<td>100%</td>
<td>100%</td>
<td>3</td>
</tr>
<tr>
<td>D</td>
<td>33%</td>
<td>50%</td>
<td>5</td>
</tr>
<tr>
<td>E</td>
<td>9%</td>
<td>64%</td>
<td>16</td>
</tr>
<tr>
<td>F</td>
<td>63%</td>
<td>79%</td>
<td>22</td>
</tr>
</tbody>
</table>

Weighted average for all six cytopathologists: 68%


Case

52 year old woman found on cervical spine MRI to have an incidental 1.5 cm thyroid nodule. No known h/o thyroid disease and otherwise healthy. No meds. Non-smoker, no history of radiation exposure. Family history negative. Nodule not palpable and no cervical LAN. TSH normal FNA result comes back AUS/FLUS or SFN.

Would you consider molecular testing?

a) I have ordered molecular testing in this situation or my patients have gotten it
b) All my patients have FNA with molecular testing
c) I would consider ordering molecular testing in this case
d) I would not order molecular testing
e) What is molecular testing?

**Affirma Gene Classifier (Veracyte)**

- mRNA gene expression, microarray
- Rule out cancer
- NPV 93-96%, sensitivity 92%, specificity 52%
- Negative test no surgery but still will miss 8% of cancers
- $475-4875

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**ThyroGenX/ThyroMIR**

- Multiplex PCR with sequence specific probes
- Specific gene mutation/translocation
  - (BRAF, RAS, RET/PTC, PAX8/PPARγ)
- Rule in test
- High PPV, low NPV
- If negative, reflexes to ThyroMIR
  - MicroRNA expression
  - Good NPV and PPV when combined with ThyGenX
- $3300 for combo test and $1675 ThyGenX alone

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**ThyroSeq**

- Next generation sequencing
- Specific gene mutation/translocation
- High NPV and PPV but very limited validation data
- $3200
Molecular Testing
Change in Practice?

• Retrospective review pre and post Affirma testing in a high volume center
• After introduction of Affirma there was a significant increase in diagnosis of AUS/FLUS and SFN with a decrease in benign findings
• No changes in institutional thyroid surgery rates or malignancy yield


What are Endocrinologists doing?
Post FNA Follow Up

• Non-Diagnostic or Unsatisfactory
  – Repeat FNA
  – Repeated non-diagnostic, high suspicion on US, take out
  – If cyst fluid only, repeat only if worrisome US features

• Malignancy
  – To the OR for total thyroidectomy

Post FNA Follow Up

• Benign
  – Least aggressive approach: no f/u
  – ATA: High suspicion US pattern, repeat US and FNA in one year
  – ATA: Intermediate to low suspicion US pattern, repeat US 12-24 months *weak, low quality evidence*
    • If growth or new worrisome features, repeat FNA
    • Or just repeat US some time
  – ATA: Low suspicion US pattern, don’t repeat US sooner than 24 months
  – Repeat FNA if > 4 cm?

• Benign x 2 – LEAVE ALONE!

Post FNA Follow Up

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• Benign x 2 – LEAVE ALONE!
## Thyroid Pathology

*The Bethesda System*

- **AUS/FLUS**
  - Surgery
  - Repeat FNA
  - Consider molecular testing
- **Follicular Neoplasm/Suspicious for Follicular Neoplasm**
  - Surgery
  - Consider molecular testing
- **Suspicious for malignancy**
  - Surgery
  - (Consider molecular testing)

## Value of a Test

1. Diagnostic performance and efficacy
   - Sensitivity, specificity, PPV, NPV, ROC, LR
2. Treatment efficacy
   - Proportion of cases helps planning treatment, proportion where treatment is changed after test
3. **Patient outcomes**
   - Proportion of tested patients who improve versus untested
   - Decrease in incidence of morbidities in tested versus untested
4. Safety
5. Cost Effectiveness

## Tips for Primary Care

- Find a good endocrinologist to work with if you can to refer to do FNA of nodules
- For ultrasound
  - Read the body of the report as well as the “impression”
  - Look for microcalcifications, solid, hypoechoic, size greater than 2 cm as worrisome features
  - Spongiform or pure cyst is not worrisome
- For FNA
  - If it is benign or cancer, you’re probably good
  - If it is indeterminate, refer to endo if you can
  - If not consider molecular testing (not just for genetics but for path) and consider US and clinical scenario
Putting it all Together

• US, FNA and Cytology are imperfect and exceedingly operator dependent.
• Despite that, thyroid cancer mortality is not significantly on the rise and is exceedingly small
• Don’t sweat the small stuff
• We need better ways to find the bad actors
• You get to actually play doctor (clinician)

When to Get an Ultra Sound

• Clear palpable abnormality
• PET positive thyroid nodule
• Abnormal imaging

For PCP and Endo

3. Don’t routinely order [or perform] a thyroid ultrasound in patients with abnormal thyroid function tests if there is no palpable abnormality of the thyroid gland.
Trend in the Number of Operations for Thyroid Cancer in South Korea, 2001–2015.