Thyroid Update

Timothy C. Petersen, MD, ECNU
About Me

- TPMG Coastal Endocrinology
  - Virginia Beach, VA

- Board Certified
  - Endocrinology, Diabetes, and Metabolism
  - Internal Medicine

- ECNU Certified
  - Endocrine Certification in Neck Ultrasound
  - American Association of Clinical Endocrinologists

- EVMS
  - Medical School
  - Residency
  - Fellowship
Disclosures

- None
Overview

- Objectives
  - Discuss commonly encountered thyroid diseases
    - Hypothyroidism
    - Thyroid nodules
    - Thyroid cancer
  - Provide updates in diagnosis and management

- Scope: adults only (18 + years old)
Outline

I. Hypothyroidism
II. Thyroid Nodules
III. Thyroid Cancer
IV. References
V. Questions
Outline

I. Hypothyroidism
II. Thyroid Nodules
III. Thyroid Cancer
IV. References
V. Questions
Timeline of Treatment Trends for Hypothyroidism

1870s
- Recognition of clinical syndrome: myxedema

1909
- Early diagnostic markers described

1916
- BMR ranges classified in hypothyroidism

1925
- Thyroxine administered as IV therapy

1926
- Thyroxine chemical structure identified

1949
- Synthesis of l-thyroxine described

1952
- T₃ discovered

1955
- First branded l-thyroxine

1970
- Peripheral T₄-to-T₃ conversion discovered
- Early treatment trials
- TSH RIA

1971
- T₃ RIA

1972
- T₄ RIA

1880s to 1920s
- Thyroidectomies cause myxedema

1930s to 1970s
- 1940s
  - Serum protein-bound iodine measured

1970 to Current

McAninch and Bianco, Annals Int Med 2016
Recognition of clinical syndrome: myxedema

1870s

1880s
- Thyroidectomies cause myxedema

1900s to 1920s

1914
- BMR measurements

1925
- Thyroxine administered as IV therapy

1926
- Thyroxine chemical structure identified

1930s
- Early treatment trials (1950s to 1960s)

1930s to 1970s

1952
- T₃ discovered

1955
- First branded l-thyroxine

1970
- Peripheral T₄-to-T₃ conversion discovered

1970 to Current

1971
- TSH RIA

1972
- T₃ RIA

1973
- T₄ RIA

LEGEND
- Thyroid transplant
- Thyroid extract
- Thyroid gland feeding
- DT
- TG
- l-thyroxine + l-triiodothyronine
- l-triiodothyronine
- l-thyroxine
Timeline of Treatment Trends for Hypothyroidism

- 1870s: Recognition of clinical syndrome: myxedema
- 1880s: Thyroxine chemical structure identified
- 1909: Early diagnostic markers described
- 1916: BMR ranges classified in hypothyroidism
- 1925: Thyroxine administered as IV therapy
- 1926: Thyroxine chemical structure identified
- 1949: Synthesis of l-thyroxine described
- 1955: First branded l-thyroxine
- 1960s: Early treatment trials
- 1970: Peripheral T₄-to-T₃ conversion discovered
- 1971: TSH RIA
- 1973: T₃ RIA

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1909: Early diagnostic markers described

1916: BMR ranges classified in hypothyroidism

1926: Thyroxine chemical structure identified

1925: Thyroxine administered as IV therapy

1949: Synthesis of l-thyroxine described

1952: T3 discovered

1955: First branded l-thyroxine

1940s: Serum protein-bound iodine measured

1970: Peripheral T4-to-T3 conversion

1970: Early treatment trials 1950s to 1960s

1971: TSH RIA

1972: T4 RIA

1880s to 1920s: Thyrotectomies cause myxedema

1930s to 1970s: NATURAL

1940s: BMR measurements

1950s to 1960s: SYNTHETIC

1970 to Current: SYNTHETIC

LEGEND:
- Thyroid transplant
- Thyroid extract
- Thyroid gland feeding
- DT
- TG
- l-thyroxine + l-triiodothyronine
- l-triiodothyronine
- l-thyroxine
Hypothyroidism

- Diagnosis
  - Symptoms/signs
  - Biochemical/lab

Source: US National Library of Medicine
January 2016: Thyroid Month: Beware of Biotin

BY ERIC SEABORG | JAN 2016

More patients are taking the dietary supplement biotin, which could be throwing off a number of test results from thyroid cancer to Graves’ disease.

Source: endocrinereview.endocrine.org
Hypothyroidism

Treatment

- Levothyroxine e.g. Synthroid/Levoxyl/Tirosint
- Liothyronine e.g. Cytomel
- Combination
  - L-thyroxine + liothyronine
  - Compounded
  - Natural desiccated thyroid e.g. Armour, Nature-Throid

Hennessey JV, Endocr Pr 2015
Hypothyroidism

- Treatment
  - Levothyroxine remains standard
    - Generic vs brand?
  - However..
    - “Individualized therapy”
    - Thr92AlaD2

McAninch, Bianco AIM 2016.
ATA 2014 Guidelines
Wartofsky *Curr Opin Diab Endo Obes* 2013
<table>
<thead>
<tr>
<th></th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>substrate molecule</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Preferred substrate</td>
<td>rT₃ &gt; T₄</td>
<td>T₄ &gt; rT₃</td>
<td>T₃ &gt; T₄</td>
</tr>
<tr>
<td>Predominant tissue</td>
<td>Liver, kidney, thyroid</td>
<td>Pituitary gland, CNS, BAT, skin, heart</td>
<td>CNS, skin, placenta, tumors</td>
</tr>
<tr>
<td>localization</td>
<td></td>
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<tr>
<td>Subcellular localization</td>
<td>Plasma membrane</td>
<td>Endoplasmic reticulum</td>
<td>Plasma membrane, nuclear membrane</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>↓</td>
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<td>↓</td>
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<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Km (T₄)</td>
<td>2μM</td>
<td>2 nM</td>
<td>37 nM</td>
</tr>
<tr>
<td>Selective activator</td>
<td>none</td>
<td>cAMP</td>
<td>Hypoxia/HIF-1</td>
</tr>
<tr>
<td>Selective inhibitor</td>
<td>PTU</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Main role in thyroid</td>
<td>Contributes to approximately 20% of</td>
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<td>Main contributor to the clearance of</td>
</tr>
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<td>hormone economy and</td>
<td>extrathyroidal T₃ production in athero-</td>
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<td>T₃; decreases intracellular T₃ levels</td>
</tr>
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<td>signaling</td>
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BAT, brown adipose tissue; CNS, central nervous system; Km, substrate concentration at which the reaction rate is half maximum velocity; HIF-1, hypoxia-inducible factor 1; rT₃, reverse triiodothyronine; T₃, triiodothyronine; T₄, thyroxine.

Source: Jonklaas et al. Thyroid 2014
### Table 3. Main Properties and Roles of Iodothyronine Deiodinases Found in Human Tissues

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Source: Jonklaas et al. Thyroid 2014
Hypothyroidism

Transplant
Hypothyroidism

Transplant

SC, IM, IV
Hypothyroidism

PO

Transplant

SC, IM, IV
Hypothyroidism

- Desiccated
- PO
- SC, IM, IV
- Transplant
Hypothyroidism

- Desiccated
- Synthetic
- PO
- Transplant
- SC, IM, IV
Hypothyroidism

- Personalized?
- Desiccated
- Synthetic
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- SC, IM, IV
Hypothyroidism

PO

Transplant

SC, IM, IV
Hypothyroidism

PO

Transplant
(stem cells)

SC, IM, IV
### Table 1. Characteristics of Adult NHANES Participants With Normal Serum TSH Levels, by Levothyroxine Use

<table>
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<th>LT₄-Treated (n = 469)</th>
<th>Matched Controls (n = 469)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>64.3 ± 14.1</td>
<td>64.1 ± 14.0</td>
<td>.88</td>
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<tr>
<td>Female (%)</td>
<td>360 (77)</td>
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<td>Race (%)</td>
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<td>Hispanic</td>
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<tr>
<td>Other</td>
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<td>Serum TSH (mIU/liter)</td>
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<sup>a</sup> P values calculated using Student t-test for continuous variables and chi-square test for categorical variables.

Petersen, McAninch, Bianco. JCEM 2016
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Petersen, McAninch, Bianco. JCEM 2016
Selenium Supplementation Significantly Reduces Thyroid Autoantibody Levels in Patients with Chronic Autoimmune Thyroiditis: A Systematic Review and Meta-Analysis

Johanna Wichman, Kristian Hillert Winther, Steen Joop Bonnema, and Laszlo Hegedüs
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>WMD (95% CI)</th>
<th>Weight</th>
</tr>
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<tr>
<td>3 months</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>de Farias</td>
<td>2015</td>
<td>-447.00 (-973.55, 79.55)</td>
<td>3.03</td>
</tr>
<tr>
<td>Krysiak study B</td>
<td>2012</td>
<td>-271.00 (-361.85, -180.15)</td>
<td>27.93</td>
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<tr>
<td>Anastasilakis</td>
<td>2012</td>
<td>-26.00 (-395.50, 343.50)</td>
<td>5.68</td>
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<tr>
<td>Karanikas</td>
<td>2008</td>
<td>-22.00 (-291.61, 247.61)</td>
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<td>Turker</td>
<td>2006</td>
<td>-201.00 (-387.42, -14.58)</td>
<td>15.43</td>
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<tr>
<td>Duntas</td>
<td>2003</td>
<td>-376.00 (-599.59, -152.41)</td>
<td>12.27</td>
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<tr>
<td>Gartner</td>
<td>2002</td>
<td>-384.00 (-485.63, -282.37)</td>
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<tr>
<td>Subtotal (I-squared = 45.4%, p = 0.089)</td>
<td></td>
<td>-270.77 (-366.35, -175.18)</td>
<td>100.00</td>
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<tr>
<td>6 months</td>
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<tr>
<td>Krysiak study B</td>
<td>2012</td>
<td>-550.00 (-638.55, -461.45)</td>
<td>53.33</td>
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<td>Anastasilakis</td>
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<td>-153.00 (-577.72, 271.72)</td>
<td>10.19</td>
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<td>Duntas</td>
<td>2003</td>
<td>-440.00 (-603.26, -276.74)</td>
<td>36.48</td>
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<tr>
<td>Subtotal (I-squared = 52.4%, p = 0.123)</td>
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<td>-469.43 (-616.83, -322.02)</td>
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<tr>
<td>12 months</td>
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<tr>
<td>Balasz</td>
<td>2008</td>
<td>-423.00 (-449.81, -396.19)</td>
<td>100.00</td>
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<tr>
<td>Subtotal</td>
<td></td>
<td>-423.00 (-449.81, -396.19)</td>
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NOTE: Weights are from random effects analysis
### 3 months

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<tr>
<td>Pilli</td>
<td>2015</td>
<td>-335.25 (-686.49, 15.99)</td>
<td>10.54</td>
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<td>Eskes</td>
<td>2014</td>
<td>-83.00 (-1022.76, 856.76)</td>
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<td>Krysiak study A</td>
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<td>-540.00 (-661.57, -418.43)</td>
<td>87.99</td>
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<tr>
<td>Subtotal</td>
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<td>-511.69 (-625.72, -397.65)</td>
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**Note:** (I-squared = 0.0%, p = 0.372)

### 6 months

<table>
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<th>Author</th>
<th>Year</th>
<th>WMD (95% CI)</th>
<th>Weight</th>
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<tr>
<td>Pilli</td>
<td>2015</td>
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<td>Nacamulli</td>
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**Note:** (I-squared = 96.9%, p = 0.000)

### 12 months

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**Note:** (I-squared = 22.9%, p = 0.255)

**NOTE:** Weights are from random effects analysis.
Hypothyroidism

- **Surgery?**
  - Ivar Gulsvog, MD, PhD
  - Prospective, randomized trial | 2012-2015
  - **Groups**
    - Control: medical therapy
    - Experimental: *total thyroidectomy*
  - **Outcomes**
    - Antibodies
    - Symptoms
Hypothyroidism

- Surgery?
  - Outcomes

<table>
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<tr>
<th></th>
<th>Medical</th>
<th>Surgical</th>
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<tr>
<td>Antibodies:</td>
<td>3200</td>
<td>2500</td>
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<tr>
<td>Symptoms:</td>
<td>85%</td>
<td>75%</td>
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Hypothyroidism

- Surgery?
  - Outcomes

<table>
<thead>
<tr>
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<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibodies:</td>
<td>3200 → 2500</td>
<td>2500 → &lt;500</td>
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<tr>
<td>Symptoms:</td>
<td>85% → 75%</td>
<td>84% → 34%*</td>
</tr>
</tbody>
</table>

* p < 0.001
Hypothyroidism

- **Surgery?**
  - **Outcomes**
    - Antibodies: 3200 $\rightarrow$ 2500
    - Symptoms: 85% $\rightarrow$ 75%
  - **Medical**
  - **Surgical**
    - 2500 $\rightarrow$ <500
    - 84% $\rightarrow$ 34%

- **Conclusion?**
Hypothyroidism

- Surgery?
  - Outcomes
    - Antibodies: 3200 → 2500  
      2500 → <500
    - Symptoms: 85% → 75%  
      84% → 34%

- Conclusion?
  - Hypothyroidism is a surgical illness.
Hypothyroidism

• Surgery?
  • Outcomes
    • Antibodies: 3200 → 2500
    • Symptoms: 85% → 75%

• Conclusion?
  • Hypothyroidism is a surgical illness. Maybe.
Outline

I. Hypothyroidism

II. **Thyroid Nodules**

III. Thyroid Cancer

IV. References

V. Questions
Thyroid Nodules

- Epidemiology
  - 50-60% all adults > 50 years old
  - 5% of all thyroid nodules = malignancy
  - Increasing incidence
    - Overdiagnosis?

ATA 2015: Nodule Sonographic Pattern Risk of Malignancy

- **High Suspicions (70-90%)**
  - Microcalcifications, hypoechoic nodule, irregular margins
  - Hypoechoic, taller than wide
  - Hypoechoic, irregular margins, extrathyroidal extension
  - Hypoechoic, interrupted rim calcification with soft tissue extrusion
  - Nodule with irregular margins, suspicious left lateral lymph node

- **Intermediate Suspicions (10-20%)**
  - Hypoechoic solid regular margin

- **Low Suspicions (5-10%)**
  - Hyperechoic solid regular margin
  - Isoechoic solid regular margin
  - Partially cystic with eccentric solid area

- **Very Low Suspicions (<3%)**
  - Spongiform
  - Partially cystic no suspicious features

- **Benign (<1%)**
  - Cyst

Haugen et al. Thyroid; October 2015
**Very low Suspicion**

<sponiform>

**partially cystic no suspicious features**

**partially cystic no suspicious features**

**Benign**

<cyst>

<1%
Low Suspicion 5-10%

hyperechoic solid regular margin

isoechoic solid regular margin

partially cystic with eccentric solid area

partially cystic with eccentric solid areas
Intermediate Suspicion
10-20%

hypoechoic solid regular margin

hypoechoic solid regular margin
High Suspicion
70-90%

- microcalcifications, hypoechoic nodule, irregular margin
- hypoechoic, irregular margins
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---

Haugen et al. Thyroid; October 2015
Where’s the Doppler?

ATA 2015: Nodule Sonographic Pattern Risk of Malignancy

Haugen et al. Thyroid; October 2015
Thyroid Nodules

- Options
  - FNA
  - Observation
  - Surgery
Thyroid Nodules

- Options
  - FNA
  - Observation
  - Surgery
  - Referral to your friendly neighborhood endocrinologist
The Bethesda System for Reporting Thyroid Cytopathology

<table>
<thead>
<tr>
<th>Bethesda diagnostic category</th>
<th>British Thyroid Association</th>
<th>American Thyroid Association</th>
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<tr>
<td>I</td>
<td>Thy1</td>
<td>Non-diagnostic/unsatisfactory</td>
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<td>Non-diagnostic or unsatisfactory</td>
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<td></td>
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<tr>
<td>II</td>
<td>Thy2</td>
<td>Benign</td>
</tr>
<tr>
<td>Benign</td>
<td>Non-neoplastic</td>
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<tr>
<td>III</td>
<td>Thy3a</td>
<td>Indeterminate or suspicious for malignancy</td>
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<td>Atypia of undetermined significance or follicular lesion of undetermined significance</td>
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<td>IV</td>
<td>Thy3f</td>
<td>Indeterminate or suspicious for malignancy</td>
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<td>Follicular neoplasm or suspicious for a follicular neoplasm</td>
<td>Follicular neoplasm suspected</td>
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<td>V</td>
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<td>Suspicious for malignancy</td>
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<td>VI</td>
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<td>Diagnostic of malignancy</td>
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Source: BMJ Best Practice
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<tr>
<td>V Suspicious for malignancy</td>
<td>Indeterminate or suspicious for malignancy</td>
</tr>
<tr>
<td>VI Malignant</td>
<td>Malignant</td>
</tr>
</tbody>
</table>

Source: BMJ Best Practice
Thyroid Nodules

- Molecular Testing
  - Bethesda III (AUS/FLUS)
  - Bethesda IV (Follicular neoplasm/suspicious for FN)
Outline

I. Hypothyroidism
II. Thyroid Nodules
III. Thyroid Cancer
IV. References
V. Questions

Source: PinMart.com
Thyroid Cancer

- Epidemiology
  - 37,200 new cases of DTC 2009 → 63,000 (‘14)\(^1\)
  - Yearly incidence 4.9/100,000 → 14.3/100,000
    - Almost entirely PTC
  - Size matters
    - New PTC < 1 cm
      - 1988 – ‘89: 25%
      - 2008 – ‘09: 39%
  - Predicted to be 3\(^{rd}\) most common cancer dx in 2019\(^2\)

\(^1\)Haugen et al. *Thyroid* 2016

\(^2\)Aschebrook-Kilfoy *Canc Epid Biomark Prev* 2013
Thyroid-Cancer Incidence and Related Mortality in South Korea, 1993–2011.

Data on incidence are from the Cancer Incidence Database, Korean Central Cancer Registry; data on mortality are from the Cause of Death Database, Statistics Korea. All data are age-adjusted to the South Korean standard population.
### Estimated New Cases Of Cancer 2017, Virginia

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Virginia</th>
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<tbody>
<tr>
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<tr>
<td>Lung and bronchus</td>
<td>5,400</td>
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<tr>
<td>Prostate</td>
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<td>Colorectum</td>
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<td>Melanoma of the skin</td>
<td>2,500</td>
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<td>Urinary bladder</td>
<td>1,870</td>
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<td>Non-Hodgkin lymphoma</td>
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<td>Kidney and renal pelvis</td>
<td>1,600</td>
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<td>Thyroid</td>
<td>1,590</td>
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Source: American Cancer Society
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<td>Thyroid</td>
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</tbody>
</table>
Thyroid Cancer

- Shifts in Perspective
  - Incidence increases; mortality doesn’t
  - Augmenting QOL, limiting damage: clinical judgment
    - Adverse effects
      - Surgery
      - Radioactive iodine
  - Likelihood for declaring bankruptcy
    - All cancer: $> 2.5x$
    - Thyroid cancer: $3.5x$

Aschebrook-Kilfoy Canc Epid Biomark Prev 2013
Thyroid Cancer

- Options
  - Surgery
    - Lobectomy vs total thyroidectomy
Thyroid Cancer

- Options
  - Surgery
    - Lobectomy vs total thyroidectomy
  - Observation
Thyroid Cancer

- Options
  - Surgery
    - Lobectomy vs total thyroidectomy
  - Observation
  - Referral to your friendly neighborhood endocrinologist
Thyroid Cancer

- Surgery, then what?
  - Radioactive iodine
  - **Suppressive** levothyroxine?
  - Tyrosine kinase inhibitors
  - Monitoring
Thyroid Cancer

- Types
  - Differentiated
  - Medullary
  - Anaplastic
  - Primary thyroid lymphoma
Thyroid Cancer

- Types
  - Differentiated
    - Papillary
    - Follicular
    - Hurthle cell
  - Medullary
  - Anaplastic
  - Primary thyroid lymphoma
Thyroid Cancer

- Types
  - Differentiated
    - Papillary
    - NIFTP
    - Follicular
    - Hurthle cell
Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma
A Paradigm Shift to Reduce Overtreatment of Indolent Tumors
January 2016: Thyroid Month: Who Let the Dogs Out?

BY GLENDA FAUNTLEROY  |  JAN 2016

Much cheaper, less invasive, and whole lot cuter than a fine-needle aspiration biopsy, thyroid cancer-sniffing dogs have a remarkable success rate. But will the medical community — as well as patients — accept these canine diagnosticians?

They spotted him wandering around the parking lot of local shopping center. The stray German Shepherd mix was in poor health and searching for food when Arny Ferrando, PhD,
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Thyroid Cancer

Before the pilot test, Frankie was imprinted with urine, blood, and thyroid tissue obtained from several different patients with metastatic thyroid carcinoma. He was then trained over six months to decipher between urine from thyroid cancer patients and those without cancer. Then, in a first-of-its-kind project, he was asked to “diagnose” the presence or absence of cancer in the urine of 34 patients who initially presented to UAMS with ≥ 1 thyroid nodule(s).

Frankie’s cues were simple: lay down if it’s cancer. Turn away if it’s benign.

He matched 30 out of 34 samples (88.2% accuracy, two false negatives, two false positives). The sensitivity was 86.7% with a specificity of 89.5%.

The use of dogs like Frankie to detect thyroid cancer could make a big impact on the medical community by relieving patients of the burden of uncomfortable and expensive diagnostic tests, Ferrando says.

Elizabeth Pearce, MD, a thyroid specialist at Boston Medical Center, agreed with the potential. “This study is highly novel, and the concept of a noninvasive, rapid, inexpensive test is quite appealing and might be of particular use on low-resource settings,” she says.

“The reported sensitivity and specificity are fairly robust relative to fine needle aspiration biopsy,” she adds. “We routinely make use of dog’s olfactory prowess in other potentially life-and-death situations, for example, bomb-sniffing, so I don’t think that the eventual use of this testing is beyond the realm of possibility.”
Summary

- Hypothyroidism
- Thyroid Nodules
- Thyroid Cancer
Outline

I. Hypothyroidism

II. Thyroid Nodules

III. Thyroid Cancer

IV. References

V. Questions
References


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Questions?
Thank you.