Thyroid Nodules and Differentiated Thyroid Cancer in Children and Adolescents: Moving Beyond Survival

Andrew J. Bauer, M.D., F.A.A.P.

Statement of Disclosure

I have nothing to disclose
No Financial Interests
No off Label experimental or investigational medications or therapies

The opinions or assertions contained in this presentation are the private views of the author and are not to be construed as reflecting the views of the WRNMMC, the U.S. Army, or the DOD.

A Buffalonian

1965-1993
• 1983 Amherst HS
• 1984 Enlisted
• 1989 Canisius College
• 1993 SUNY Buffalo and started active duty

A Buffalonian

Mission

At the conclusion of the lecture, attendants will be able to:
1. Discuss the incidence and risk factors associated with developing thyroid nodules and/or differentiated thyroid cancer.
2. Define the common presentation for thyroid nodules in children and adolescents.
3. Discuss the approach to evaluation and treatment of thyroid nodules in children and adolescents.
4. Recognize the importance of establishing pediatric specific clinical practice guidelines, establishing regional centers for evaluation and care, and the need for multi-center, collaborative studies.
Rules of Engagement

• Coffee, questions and comments are encouraged and welcomed

Exit Strategy

• At 0900hrs, ET, my mission is over and you are free to enjoy the rest of the day and upcoming weekend

The Focus of Discussion

Orientation

Normal

Thyroid Nodules and Thyroid Cancer are not rare
Between 1973 and 2006, a doubling in incidence of thyroid cancer was observed in the United States, Canada, France, Australia, and other countries. Studies by Kent et al. (CMAJ 2007), Colonna et al. (Eur J Cancer 2007), Burgess et al. (Thyroid 2002), and Davies et al. (JAMA 2006) have contributed to our understanding of this trend.

Review Article
Worldwide Increasing Incidence of Thyroid Cancer: Update on Epidemiology and Risk Factors

Pediatrics vs Adults
Has there been an increase in the incidence of thyroid cancer in children and adolescents?
Pediatric Thyroid Cancer? Incidence Rates 2000-2007

**Pediatric Thyroid Cancer Incidence Rates 2000-2007**

- **Incidence of TC in 15-19 is > than NHL 2007: 18/million TC vs 12/million NHL**

**Thyroid Cancer ~ 7% of cancers diagnosed in 15-19 yr old**

Pediatric Thyroid Cancer National Cancer Data Base

- 3,933 patients < 18 years of age diagnosed with Thyroid Cancer between 1985 and 2007
- 2nd most common cancer in Caucasian girls 15-19 years old

"Pediatrics vs Adults"

Has there been an increase in the incidence of thyroid cancer in children and adolescents?  

= Yes
**Pediatrics vs Adults**

Same or Distinct disease?

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**Similarities** compared to adult patients...

1. Clinical Presentation
2. US features
3. Cytological features

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**Similarities** compared to adult patients...

1. Clinical Presentation
2. US features
3. Cytological features

---

**Similarities** compared to adult patients...

1. Clinical Presentation
2. US features
3. Cytological features
4. Histological features* 

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**Thyroid Carcinoma**

- **Subtypes**
  - Differentiated Thyroid Carcinoma
  - Follicular Thyroid Carcinoma

- 5-10% of DTC in Pediatrics
- Histologic Diagnosis
- Indeterminate Cytology
- FA vs FTC
- Decreased incidence of regional metastasis
Thyroid Carcinoma

- Subtypes
  - Differentiated Thyroid Carcinoma
    - Follicular Thyroid Carcinoma
  - Papillary Thyroid Carcinoma

Differentiated Thyroid Carcinoma
- 5-10% of DTC in Pediatrics
- Histologic Diagnosis
  - Indeterminate Cytology
  - FA vs FTC
  - Decreased incidence of regional metastasis

Follicular Thyroid Carcinoma
- Decreased incidence of regional metastasis

Papillary Thyroid Carcinoma
- 90-95% of DTC in Pediatrics
- Variants
  - Classic
  - Solid
  - Diffuse Sclerosing PTC
  - Follicular Variant of PTC
  - Encapsulated
  - Poorly circumscribed, Infiltrative Subtype
  - Majority have regional metastasis

Now 15yrs old
- Feb 2010 – TT, CND, LLND
  - 5.6cm dominant nodule
  - Extensive angiolymph invasion
  - CND – 20/27+
  - LLND – 3/9+
  - L Level V – 4/16+
- Oct 2010 – RLND
- PFTs – mild diffusion impairment

Similarities compared to adult patients...
1. Clinical Presentation
2. US features
3. Cytological features
4. Histological features
5. Bio/Tumor marker
   - Thyroglobulin (Tg)
   - Always interpreted with
     - TSH – basal vs stimulated → increased NIS and Tg
     - Anti-Tg

Differences compared to adult patients...
1. Oncogene prevalence

Similarities compared to adult patients...
1. Clinical Presentation
2. US features
3. Cytological features
4. Histological features
5. Signaling pathway activation

Differences compared to adult patients...

<table>
<thead>
<tr>
<th>Gene rearrangements</th>
<th>Children and adolescents (%)</th>
<th>Adults (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET/PTC</td>
<td>30-67</td>
<td>0-26</td>
</tr>
<tr>
<td>NTRK</td>
<td>8-11</td>
<td>8-13</td>
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<tr>
<td>AXL/PDGFR-GRB</td>
<td>11 (Bone-Chondro, short stature)</td>
<td>1</td>
</tr>
<tr>
<td>HRAS</td>
<td>Unknown</td>
<td>0-6%</td>
</tr>
<tr>
<td>Point mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JAK2 fusions</td>
<td>0-8</td>
<td>0-11</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>0-13</td>
<td>0-13</td>
</tr>
<tr>
<td>PI3K</td>
<td>0-23</td>
<td>0-23</td>
</tr>
</tbody>
</table>
**Differences** compared to adult patients…

Differences compared to adult patients…

**Oncogene prevalence**

- **BRAF vs RET/PTC**

1. **Diagnostic Implications**
   1. Ease of testing
   2. Specificity

1. **Prognostic Implications**

**Progressive adult thyroid cancer**

**Dedifferentiated disease**

- 67yo TSVPTC

- 41yo poorly differentiated TC

**Differentiated Thyroid Cancer in Children and Adolescents**

- Maintain NIS expression
- May develop persistent, stable disease

**Presentation**

**Clinical Differences** compared to adult patients…

- Thyroid nodules

**Thyroid Nodules**

**Prevalence and Age**
Thyroid Nodules
Incidence and Prevalence

Prevalence of palpable thyroid nodules in children = 1 to 2%

<table>
<thead>
<tr>
<th>Method</th>
<th>Prevalence</th>
<th>Age</th>
<th>N</th>
<th>Location</th>
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<tbody>
<tr>
<td>Palpation</td>
<td>2%</td>
<td>11-18</td>
<td>5,179</td>
<td>UT, NV, AZ</td>
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<tr>
<td>Palpation</td>
<td>1%</td>
<td>school age</td>
<td>3,949</td>
<td>N. Italy</td>
</tr>
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</table>

*Rallison et. al, JAMA 1975    *Chiesa et. al Annals Onc 2004

Thyroid Nodules
Children and Adolescents
Incidental thyroid abnormalities identified on neck US for non-thyroid disorders
Shivaram Avula et. al Pediat Radiol (2010) 40:1774-1780

N = 1,228 neck US (mean age = 8.1 years)
18% found to have a cyst or nodule

Thyroid Nodule Risk of Malignancy

Adults = 5-10%

Risk of Malignancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>%</th>
<th>Reference</th>
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<tbody>
<tr>
<td>1</td>
<td>68/386</td>
<td>50.0</td>
<td>Hyams et al (1962)</td>
</tr>
<tr>
<td>2</td>
<td>76/394</td>
<td>25.4</td>
<td>Adams (1967)</td>
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<td>3</td>
<td>12/209</td>
<td>58.0</td>
<td>Hintz et al (1972)</td>
</tr>
<tr>
<td>4</td>
<td>9/84</td>
<td>41.0</td>
<td>Scott &amp; Carver (1974)</td>
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<tr>
<td>5</td>
<td>1/164</td>
<td>63.2</td>
<td>Veal et al (1974)</td>
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<td>6</td>
<td>1/258</td>
<td>37.7</td>
<td>O’Toole et al (1998)</td>
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<td>7</td>
<td>1/197</td>
<td>45.7</td>
<td>Boldt et al (1998)</td>
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<tr>
<td>8</td>
<td>1/155</td>
<td>55.9</td>
<td>Power et al (1998)</td>
</tr>
<tr>
<td>9</td>
<td>1/221</td>
<td>37.0</td>
<td>Roy et al (2001)</td>
</tr>
<tr>
<td>10</td>
<td>1/125</td>
<td>21.7</td>
<td>Almeida et al (2001)</td>
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<tr>
<td>11</td>
<td>1/196</td>
<td>51.3</td>
<td>Bentz et al (2001)</td>
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<tr>
<td>12</td>
<td>1/231</td>
<td>38.5</td>
<td>Szwarc et al (2001)</td>
</tr>
<tr>
<td>13</td>
<td>1/237</td>
<td>41.8</td>
<td>Nyiri et al (2001)</td>
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<tr>
<td>14</td>
<td>1/287</td>
<td>26.0</td>
<td>Convit et al (2001)</td>
</tr>
<tr>
<td>16</td>
<td>1/366</td>
<td>49.0</td>
<td>McCartney et al (2001)</td>
</tr>
<tr>
<td>17</td>
<td>1/155</td>
<td>64.0</td>
<td>Sekine et al (2001)</td>
</tr>
<tr>
<td>18</td>
<td>1/234</td>
<td>49.0</td>
<td>Nishida et al (2001)</td>
</tr>
<tr>
<td>19</td>
<td>1/256</td>
<td>30.7</td>
<td>Hatazawa et al (2001)</td>
</tr>
<tr>
<td>20</td>
<td>1/228</td>
<td>34.3</td>
<td>Hatazawa et al (2001)</td>
</tr>
<tr>
<td>21</td>
<td>1/215</td>
<td>12.9</td>
<td>Sekine et al (2001)</td>
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<tr>
<td>22</td>
<td>1/228</td>
<td>30.7</td>
<td>Nishida et al (2001)</td>
</tr>
<tr>
<td>Overall</td>
<td>288/1,338</td>
<td>21.1</td>
<td></td>
</tr>
</tbody>
</table>

Histological confirmation (30 studies)
- FNAB = 722
- Histolo = 343
- Malignancy = 98/343
- 29% = 29%
- Range = 11% -> 58%

Compared to adult patients...

- Thyroid nodules are less common in pediatric patients
- Greater risk that a nodule is malignant
Thyroid Nodules Presentation

- **Most Common Presentation**
  1. Asymptomatic nodule or mass noted by parents, patient or provider

Incidental finding during non-thyroid imaging

Thyroid Nodules Presentation

- **Most Common Presentation**
  1. Asymptomatic nodule or mass
  2. Incidental or serendipitous finding

DICER1 Mutations in Familial Multinodular Goiter With and Without Ovarian Sertoli-Leydig Cell Tumors

DICER1 Pleuropulmonary Blastoma Familial Tumor Predisposition Syndrome

13 year old girl
- Swallowed part of her orthodontic retainer
- Noted to have tracheal deviation during retrieval

Rio Frio et al. JAMA 2011; 305(1): 68-77
Thyroid Nodules Presentation

13 year old girl
- Swallowed part of her orthodontic retainer
- US -

MRI - Large left sided thyroid mass

Thyroid Nodules Presentation

13 year old girl
- Swallowed part of her orthodontic retainer

Most Common Presentation
1. Asymptomatic nodule or mass
2. Incidental finding during non-thyroid imaging
3. Persistent cervical adenopathy

4yo Male
- Cervical adenopathy x 2 months
- Antibiotics x 1 course, no resolution
- Referred to ENT – excisional biopsy
- US

<1cm hypoechoic nodule, ill defined border, hyperechoic foci
Thyroid Nodules

Presentation

Most Common Presentation
1. Asymptomatic nodule or mass
2. Incidental or serendipitous finding
3. Persistent cervical adenopathy

- Thyroid US before excisional biopsy
- “Bulky” disease = pre-operative, anatomic imaging (CT or MRI) for surgical planning

4. Symptoms - fullness or lump, change in voice

5. Surveillance in ‘high-risk’ patients*

Thyroid Nodules

Incidence and Prevalence

Increased Risk?
Nodules and Cancer

- Age
- Gender
- Method of detection
- Iodine status
- History of
  - Ionizing Radiation exposure
  - Familial Non-Medullary TC
  - Genetic Syndromes
  - Autoimmune Thyroid disease

High Risk Groups
1. Ionizing radiation
2. FNMTC
3. Genetic syndromes
4. History of autoimmune thyroid disease

Thyroid Nodules

High Risk Groups - Ionizing Radiation

20yo male - Hx ALL and TBI @ 8 1/2 years
- Surveillance US (Mar ‘11) - 4 x 11 x 8mm solid nodule

(+/-) hypoechogenic, microcalcifications, irregular border
(+/-) Increased intranodular flow

Final Diagnosis
- PTC, left lobe and isthmus
- Extensive lymphovascular invasion and multifocal extension into perithyroidal soft tissues
- +LN 3/10 (level VI) with focal extranodal extension

No distinct palpable nodule
Thyroid Nodules
High Risk Groups - Ionizing Radiation

Ionizing radiation
RR = 1.3 per Gy up to 20 Gy

Unique Aspects to Disease in the Pediatric Population
Risk of Malignancy

Modifiers
- Female Gender
- Time since exposure
  - Risk extended over decades
- Younger the age
  - Shorter the latency
  - Higher the risk

Thyroid Nodules
Incidence and Prevalence

High Risk Groups
1. Ionizing radiation – craniospinal, TBI
   - Thyroid Screening
   - PE annually
   - US – starting 3 to 5 years

Thyroid Nodules
Incidence and Prevalence

High Risk Groups
1. Ionizing radiation
2. Familial Non-Medullary Thyroid Cancer

Medical Exposure to Radiation and Thyroid Cancer

Cancer risks following diagnostic and therapeutic radiation exposure in children
Thyroid Nodules
Incidence and Prevalence

High Risk Groups
1. Ionizing radiation
2. Familial Non-Medullary Thyroid Cancer
   a. Syndromic
   b. Non-Syndromic

Syndromic NMTC

Cowden syndrome
- Breast cancer ~30%
- Endometrial cancer 5-10%
- Thyroid Cancer 10%

BRRS
- Macrocephaly
- Lipomatosis
- Hemangiomas
- Penile freckling

PTEN Hamartoma Tumor Syndrome

Signaling pathway

PTEN hamartoma syndrome
- "Down-Drift"
  - PTEN
  - KLLN promoter hypermethylation
  - SDHx – succinate dehydrogenase* (11 variants)

* SDHx/SDD – hereditary pheochromocytoma-paraganglioma syndrome

PTEN Hamartoma Syndrome (CS, BRRS)
- Macrocephaly
- Lipomatosis
- Hemangiomas
- Penile freckling
Syndromic NMTC

PTEN hamartoma syndrome

- Genetic variants
  - PTEN+ 23%
  - KLLN promoter hypermethylation 30%
  - SDHx – succinate dehydrogenase 10%

Ni et al. AmJHumGen 2008
Bennett et al. JAMA 2010

Syndromic nmtc

CS and Thyroid Cancer

Ngeow et al. JCEM 2011

5-year, multicenter, prospective accrual of 2723 CS/CSL patients
- 664 thyroid cancers

Tables

<table>
<thead>
<tr>
<th>Group</th>
<th>Observed</th>
<th>Expected</th>
<th>RR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH</td>
<td>35</td>
<td>54</td>
<td>0.64</td>
<td>0.43-0.91</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SDHB-D</td>
<td>15</td>
<td>45</td>
<td>1.23</td>
<td>0.94-1.61</td>
<td>0.14</td>
</tr>
<tr>
<td>KLLN+</td>
<td>14</td>
<td>50</td>
<td>0.28</td>
<td>0.18-0.43</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

- 9x fold risk of pediatric onset thyroid cancer
- 5 females, 1 male
- 2-8x fold increased risk compared to SEER
- 4 cPTC, 1 FTC, 1 Hürthle Cell CA
- All PTEN+

Syndromic nmtc

CS and Pediatric Thyroid Cancer

Smith et al. JCEM 2011

5/7 PHTS patients with thyroid cancer, dx < 12yrs
- 3FTC, 1 FTC/PTC, 1mPTC
  - 3/4 males with penile freckling
  - 2/3 females with macrocephaly
  - Thyroid surveillance should begin @ dx PTEN+

Summary

- Thyroid Cancer is the most frequent incident component of PHTS
- Thyroid surveillance should begin at time of diagnosis (< 18 years of age)
Thyroid Nodules
Incidence and Prevalence

High Risk Groups
1. Ionizing radiation
2. FNMT
   a. Syndromic
      a. PTEN Hamartoma Syndrome (CNS, BRRS)
      b. Carney Complex
      c. Familial Adenomatous Polyposis
      d. PRIDICER1
   b. Non-Syndromic
      a. Familial Papillary thyroid cancer

Familial Nonmedullary thyroid Cancer

- TS – 17yo f w/PTC
- 41yr
- 43yr
- 14yo

Non-Syndromic nmtc
familial non-medullary thyroid cancer (FNMTc)

- First report – identical twins with PTC
  (Robinson and Orr, 1955)
- Definition
  - Diagnosed when ______ or more 1st degree
    relative have non-medullary TC without
    known syndromic association
    - 2 or more
    - 3 or more

Non-Syndromic nmtc
familial non-medullary thyroid cancer (FNMTc)

- Genetic inheritance
  - Autosomal dominant with incomplete penetrance
    and variable expressivity
- Candidate loci or Gene?

Thyroid Nodules
Incidence and Prevalence

High Risk Groups
1. Ionizing radiation
2. FNMT
3. Auto-immune thyroid disease
   a) Hashimoto’s Thyroiditis
   b) Graves Disease

Table # 6 familiar tumor syndrome characterized by a predominance of non-medullary thyroid carcinomas

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Incidence</th>
<th>Chromosomal</th>
<th>Candidate loci or Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTC associated with PKH</td>
<td>Unknown</td>
<td>1q11</td>
<td>Unknown</td>
</tr>
<tr>
<td>Familial NCOM with PTC</td>
<td>Unknown</td>
<td>1q11</td>
<td>Unknown</td>
</tr>
<tr>
<td>PTC</td>
<td>Unknown</td>
<td>1q11</td>
<td>Unknown</td>
</tr>
<tr>
<td>Familial TSO and without congenital defects</td>
<td>Unknown</td>
<td>1q11</td>
<td>Unknown</td>
</tr>
<tr>
<td>Familial papillary thyroid cancer (FNMTC)</td>
<td>Unknown</td>
<td>1q11</td>
<td>Unknown</td>
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</tbody>
</table>

Thyroid Nodules and Cancer in Children and Adolescents Affected by Autoimmune Thyroiditis

N= 365 (308 girls)
- Age: 3.8 to 17 years
- US performed every 1-2 years
- 31.5% found to have a nodule
  - 60% Solitary
- 3% found to have PTC (n=11)
  - Not associated with elevated TSH

US -> patient with asymmetric gland or palpable nodule
**Pseudo-Nodules**

- Right lobe
- Carotid hypoechoic, heterogeneous nodule

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**Presentation**

**Most Common Presentation**

1. Asymptomatic nodule or mass
2. Incidental or serendipitous finding
3. Symptoms - fullness or lump, change in voice
4. Other
   - Persistent cervical adenopathy
   - Autoimmune thyroid disease - Hashimoto’s or Graves’ disease

**Risk of Malignancy**

- **Histological confirmation**
  - (40 studies)
  - FNAB: 722
  - Biopsy: 343
  - Malignancy: 98/343

- **Risk of Malignancy**

  *Majority of nodules are benign*
Risk of Malignancy

Nodule = Surgery?

Thyroid Nodules in Children
Common Practice in Children

• More aggressive approach due to
  – increased risk of malignancy
  – Lack of natural history data for benign lesions
  – More difficult patient situation
    • Consent vs. Assent
    • Risk of sedation
    • Unknown psychological impact of repeated procedures and long-term burden of disease

Published rates of malignancy in operated thyroid nodules in adults vs children

<table>
<thead>
<tr>
<th></th>
<th>Benign</th>
<th>Malignant</th>
<th>Percent malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children*</td>
<td>835</td>
<td>299</td>
<td>26%</td>
</tr>
<tr>
<td>Adult</td>
<td>1329</td>
<td>1010</td>
<td>43%</td>
</tr>
</tbody>
</table>

*p=0.000-22

Published rates of malignancy in operated thyroid nodules in adults vs children

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<td>1329</td>
<td>1010</td>
<td>43%</td>
</tr>
</tbody>
</table>

Evaluation
Stratification of Risk

1. Biochemical

• 15yo female noted to have an enlarged thyroid on routine physical exam
• ROS positive for decreased exercise intolerance (cross-country runner), occasional palpitations, difficulty falling to sleep

Evaluation
Stratification of Risk

1. Biochemical

1. TSH and fT4
Evaluation
Stratification of Risk
1. Biochemical
2. Ultrasound
3. Fine Needle Aspiration Biopsy

Ultrasound
• Characteristics suggestive of Benign lesions
  – Hyperechoic pattern
  – Translucent halo
  – Smooth well-defined margin

• Characteristics associated with Malignancy
  – Hypoechoic
  – Irregular or jagged border/margins
  – Increased intranodular vascularity
  – Microcalcifications
  – Taller than wide (transverse view)

US and Pediatric Nodules

→ 25% of malignant lesions will have at least 1 benign US characteristic

→ 25% of benign lesions will have at least 1 malignant characteristic

Clinical Features to help predict the risk of malignancy
Clinical Factors to help predict the risk of malignancy

- High Risk groups
- Increased likelihood of thyroid cancer spreading to lymph nodes in the neck

Jarzab et al. Endo-Related Cancer 2005

Carty et al. Thyroid 2009

Thyroid Nodules
Risk and location of metastasis

- Most common site of metastasis
  - Central (level VI)
    - Prearyngeal (Delphian)
    - Pretracheal
    - Paratracheal

Farrag et al. World J Surg 2009

Clinical Factors to help predict the risk of malignancy

- Increased likelihood of thyroid cancer spreading to lymph nodes in the neck
- Challenge
  1. > 300 LN in the neck
  2. Increased incidence of reactive cervical adenopathy (‘swollen glands’) in pediatric patients

Reassuring Features
1. Consistency (PE)
2. Oval Shape
3. Presence of hilum
4. Central vascularity

Thyroid Nodules
Lymph Nodes

Consensus Statement on the Terminology and Classification of Central Neck Dissection for Thyroid Cancer

- Most commonly involved central LN (level VI)
  - Prearyngeal (Delphian)
  - Pretracheal
  - Paratracheal
- Most commonly involved lateral LN
  - III
  - IV
  - II-A
Concerning Features
1. Consistency (PE)
2. "Size"
3. Rounded shape
4. Absence of hilum
5. Peripheral hypoechoic areas
6. Cystic areas
7. Microcalcifications
8. Extranodal extension
9. Peripheral vascularity

Diagnostic Implication
- 2008 NCI sponsored Bethesda System for reporting thyroid cytopathology

Compared to adult patients...
- Thyroid nodules are less common in pediatric patients
- Greater risk that a nodule is malignant
  - Risk that an indeterminate FNA will be malignant?

Stratification of risk in indeterminate cytology
- **BRAF**
  - Reflexive testing in adults

Validation Tests
- Malignancy/PPV = miRInform (Asuragen)
- Benignity/NPV = Afirma (Veracyte)
Stratification of risk in indeterminate cytology

- **BRAF**
  - Reflexive testing in adults

- Validation Tests
  - Malignancy/PPC = miRInform (Asuragen) Nikiforov et al. JCEM 2010
  - Benignity/NPV = Afirma (Veracyte) Alexander et al. NEM 2012
  - Pediatrics – Lack of validation of commercially available ancillary testing

Risk of Malignancy

<table>
<thead>
<tr>
<th>Test</th>
<th>Ref.</th>
<th>Number %</th>
<th>Reference</th>
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<tbody>
<tr>
<td>FNAB</td>
<td></td>
<td>722</td>
<td></td>
</tr>
<tr>
<td>Histolo</td>
<td></td>
<td>343</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>98/343</td>
<td>29%*</td>
<td></td>
</tr>
</tbody>
</table>
| Stratified based on
  - Risk factors
  - Physical exam
  - US features
  - FNA

Treatment – how much and when?

- Surgery
  - Pre-operative imaging
  - Lobectomy/lthmusectomy vs. Total Thyroidectomy
  - Lymph node dissection
  - Prophylactic Central Neck dissection
  - Lateral neck dissection
  - Repeat Surgery

Clinical Differences Compared to Adults

Greater Burden of Disease at Diagnosis

- Loco-regional disease 30-50% vs 50-80%
- Distant metastasis – lungs ~5% vs ~15-20%

Differences in Disease Behavior Prepubertal vs Pubertal

1. High % of 're-operation'
2. Lobectomy associated with 10-fold risk of recurrence
3. Incomplete LN dissection associated with 3-fold risk of recurrence

Histological confirmation (10 studies)
- FNAB 722
- Histolo 343
- Malignancy 98/343

= 29%*
Treatment – how much and when?

- Radioiodine
  - Ablation vs Treatment
  - Empiric dosing vs dosimetry
  - Time between RAI dosing
  - Pulmonary mets
    - Evidence of progression
    - Persistent, non-progressive disease

The majority of pediatric patients do not die from thyroid cancer*

The outcome is not always favorable

Progressive adult thyroid cancer
Dedifferentiated disease

- 38yo female
  - Diagnosed PTC at 15yrs
  - s/p TTX, CLND
  - s/p 3000+ mCi RAI

8yo male with PTC

- Persistent cervical adenopathy > 6 months
- Excisional biopsy = PTC
- TT – August 31st 2010
- Post-OP CT = “massive pulmonary infiltrates”
  - No RAI administered
  - Placed on LT4 suppressive therapy (TSH < 0.01 mIU/mL)

Chest x ray August 2012
CT scan August 2012
Hypoxic 80% RA

Progressive adult thyroid cancer
Dedifferentiated disease

- 38yo female
  - Diagnosed PTC at 15yrs
  - s/p TTX, CND
  - s/p 3000+ mCi RAI
Patients ≤ 18 years
95% 30+ year survival

Disease Specific Mortality vs Disease Specific Morbidity and Disease Free Survival

95% 30+ year survival

- Increased risk of recurrent disease

Disease Free Survival

- Median follow-up = 22.6 years
- Range 1-66 years
- N = 30

~ 45% recur

32 patients recurred over 40 years of follow-up

- Increased risk of recurrent disease

Risk and impact from side effects of therapy expressed over a lifetime
Compared to adult patients...

- Lower incidence of disease is associated with
  - Centers with less experience in evaluation
  - Centers with less experience in treatment
  - Surgery performed by 'low-volume' surgeons

Pediatric endocrine Surgery:
Who is operating on our Children?

Thyroid Surgery in Children

Thyroid Carcinoma
Surgical Approach

Clinical and Economic outcomes of thyroid and parathyroid surgery in children

Second Primary Malignancy Risk
After Radioactive Iodine Treatment for Thyroid Cancer: A Systematic Review and Meta-analysis

RAI (+) vs. RAI (-)
- Absolute risk of SPM ~1% higher if treated with RAI
  - Salivary Gland Carcinoma

Risks associated with Radioactive Iodine Therapy
Non-Thyroid Second Primary Malignancy

Linear Dose effect – after adjusting for external radiotherapy

Increasing dose α increased RR
- soft-tissue and bone
- colorectal cancer

TABLE 2. Relative Risk of Second Primary Malignancy in Thyroid Carcinoma Patients Treated with Radioactive Iodine Relative to Those Not Treated with Radioactive Iodine

<table>
<thead>
<tr>
<th>Type of SPM</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>All SPM</td>
<td>1.28</td>
<td>1.18 - 1.39</td>
</tr>
<tr>
<td>Breast</td>
<td>1.91</td>
<td>0.96 - 2.79</td>
</tr>
<tr>
<td>Brain</td>
<td>0.99</td>
<td>0.64 - 1.56</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>1.74</td>
<td>0.73 - 4.17</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>1.86</td>
<td>0.72 - 4.62</td>
</tr>
<tr>
<td>Digestive tract</td>
<td>1.87</td>
<td>0.80 - 4.31</td>
</tr>
<tr>
<td>Kidney and renal pelvis</td>
<td>1.30</td>
<td>0.56 - 3.07</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.28</td>
<td>0.65 - 2.53</td>
</tr>
<tr>
<td>Lung</td>
<td>0.96</td>
<td>0.60 - 1.56</td>
</tr>
<tr>
<td>Malignant (other)</td>
<td>0.96</td>
<td>0.64 - 1.42</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.66</td>
<td>0.74 - 3.72</td>
</tr>
</tbody>
</table>

The data pooled are from the SEER study by Rosenthal et al[8] and the meta-analysis by Rosenthal et al[9]. The main difference is the inclusion of the references used in the meta-analysis.
Compared to adult patients…

- Low incidence of disease is associated with
  - Centers with less experience in evaluation
  - Surgery performed by ‘low-volume’ surgeons

- Care that is either completely in an adult center or straddled between adult and pediatric centers

Thyroid Centers of Excellence

**Multi-Disciplinary center using oncology paradigm**
1. **Ped Endo -** medical management and coordination of care
2. **Pediatric Oncology**
3. **Radiology**
   1. IR for FNA
   2. US - with expertise in thyroid and neck imaging
   3. NM - RAI and imaging
4. **Pathology** - with HUP
5. **Surgery** – “high volume surgeons” with pediatric specific ancillary support - anesthesia, ICU
6. **Oncology Social Work Services**

The Thyroid Center

**A better way forward**

<table>
<thead>
<tr>
<th>Actual</th>
<th>FY11</th>
<th>FY12</th>
<th>Projected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient New Visit</td>
<td>67</td>
<td>139</td>
<td>194</td>
</tr>
<tr>
<td>Outpatient Established Visit</td>
<td>72</td>
<td>255</td>
<td>194</td>
</tr>
<tr>
<td>New Thyroid Cancer DX</td>
<td>22</td>
<td>37</td>
<td>47</td>
</tr>
<tr>
<td>Surgery</td>
<td>26</td>
<td>66</td>
<td>70</td>
</tr>
<tr>
<td>FNA</td>
<td>28</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>Radioablation/Nuclear Medicine Scan</td>
<td>44</td>
<td>81</td>
<td>118</td>
</tr>
<tr>
<td>CT and Spec/CT</td>
<td>42</td>
<td>87</td>
<td>133</td>
</tr>
<tr>
<td>MRI</td>
<td>6</td>
<td>16</td>
<td>39</td>
</tr>
<tr>
<td>PFT</td>
<td>5</td>
<td>10</td>
<td>47</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>42</td>
<td>145</td>
<td>260</td>
</tr>
<tr>
<td>Total Diagnostic tests/treatment</td>
<td>114</td>
<td>341</td>
<td>373</td>
</tr>
</tbody>
</table>

Efforts to improve diagnosis and predict diagnosis

- **Efforts to improve diagnosis**
- **Efforts to reduce disease specific morbidity**

Efforts to reduce disease specific morbidity

**Surgical Approach to Re-operative procedures**

- **13yo swallowed retainer**
  - Total Thyroidectomy, central and left lateral ND
  - Diagnostic whole body scan – 34% uptake
- DxWBS with SPECT-CT
  - 34.5%
  - Left level II
  - Right Level VI paratracheal

- dxWBS with SPECT-CT
  - 34.5%
  - Left level II
  - Right Level VI paratracheal

Thyreoid Cancer
Re-operative Procedure
Intra-operative US with methylene blue mapping

Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer
The American Thyroid Association Guidelines Taskforce

Members: Peter Angelos, MD, PhD, Andrew J. Bauer, MD, Salvatore Benvenuto, MD, Janine M. Cerutti, PhD, Catharina J. Dinneen, MD, Gary L. Francis, MD, PhD (Chair), Jill Hamilton, MD, Ian D. Hay, MD, PhD (Board Liaison), Markus Luster, MD, Marquita T. Pursel, MD, Meredith Retchin, MD, Geoffrey S. Thompson, MD, Steven G. Waguespack MD, and Shunichi Yamashita, MD.
Questions
Moving beyond survival.....
http://chicksdigbigscars.com/