Thyroid Nodules and Differentiated Thyroid Cancers in Children
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Children’s Hospital of Richmond at Virginia Commonwealth University
Richmond, VA, USA

Objectives
- **Goal:**
  - The goal for this presentation is for the attendee to gain a better understanding of the prevalence, diagnosis and treatment of thyroid nodules and cancers in children.
- **Objectives:**
  1. By attending this presentation, you will learn the prevalence and most common presentations of thyroid nodules and cancers in children.
  2. By attending this presentation, you will learn how best to evaluate suspected thyroid nodules in children.
  3. By attending this presentation, you will learn how best to treat thyroid cancers in children and the long-term outcome of therapy.

I would like for you to remember four (4) things:
- 1. Thyroid nodules and cancers are common in children
- 2. Second most common presentation in children is persistent cervical adenopathy
- 3. 40% are discovered by parent
- 4. Radiation exposure increases the risk but IS NOT REQUIRED

Embryonic Development of the Thyroid
First Endocrine Gland to Develop
Derived From the Second Pharyngeal Arch

Embryology.med.unsw.edu.au/Notes/endocrine5.htm

DISCLOSURES
No Financial Disclosures or Conflict of Interest

Thank
Steven Waguespack MD, MD Anderson Cancer Center
for use of several slides

Refer to:
Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer
The American Thyroid Association Guidelines Task Force on Pediatric Thyroid Cancer
Thyroid, 2015; 25(7): 716-759; PMID: 25900731

TTF-1 Stimulates TPO, TG, NIS
ko Mouse: no thyroid

PAX-8 Thyroid Differentiation
ko Mouse: dysplastic gland

TTF-1 thyroid differentiation

TTF-2 Thyroid Migration
ko Mouse: thyroid gland at base of tongue

TSH-R
Expressed after thyroid descends

www.bartleby.com/107/13.html

www.moondragon.org/.../hypothyroid.html

www.bartleby.com/107/13.html

PAX-8 Thyroid Differentiation
ko Mouse: dysplastic gland

TTF-1 thyroid differentiation

TTF-2 Thyroid Migration
ko Mouse: thyroid gland at base of tongue

TSH-R
Expressed after thyroid descends

www.moondragon.org/.../hypothyroid.html
**Thyroid Hormone Synthesis**

1. Iodide trap (NIS)
2. Iodine oxidation (TPO)
3. Pendrin Transport
4. Iodination of Tg
5. Pinocytosis
6. Proteolysis of Tg
7. Deiodination to recover I
8. Stimulation by TSH

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**Objective 3: Learn to Palpate the Thyroid Better than the Parent**

**Visual Inspection First**

Palpation Softly From Behind

**THYROID STATUS EXAMINATION**

Ask patient to swallow and assess symmetry of thyroid lobe elevation (asymmetry may inspire a unilaterally thyroid mass)

Don't Forget the Lymph Nodes
Objective 1: How Common Are Thyroid Nodules in Children?

**Thyroid Nodules in Children**
- **Prevalence:** 0.2-5% vs 19-35% in adults
  - 184 nodules > 5 mm evaluated
  - 29 malignant (16%)
- **Cystic lesions occur in 57% of children**

**BUT**
- There are groups in which nodules are more common

Are there groups of children at greater risk for nodules?

**Thyroid Nodules in Cancer Survivors**
- Ontario Canada did US
  - Radiation therapy > 10 yr prior
  - 87 survivors
- US detected nodules in 59%
  - 22% 5-10 mm; 19% > 10 mm
  - 14 patients FNA
  - 6% (n = 5) had PTC
- COG recommends palpation
- ATA Pediatric Guidelines recommend palpation

**THYROID DISORDERS**

- **Hashimoto’s Thyroiditis**
  - Most common chronic Thyroiditis
  - Peak incidence in early to mid-puberty
  - Presentation
    - Symmetrical or asymmetric
    - Firm, non-tender
  - Hypothyroid:
    - Poor growth
    - Elevated lipids
    - Cool skin, cold intolerance
    - Constipation
    - Best kid in class

Li et al. Thyroid 2014; 24(12) 1796-1805
**AIT Associated Thyroid Nodules**

- 365 Children with autoimmune thyroid disease (AITD) Hashimoto’s or Graves’
  - 3.6 – 17 yr of age
- 31.5% (n = 115) Develop Thyroid Nodules
  - 60% solitary
  - 40% multiple
  - 38 Palpable
    - 28 / 115 nodules = 33% of all nodules
    - 38 / 365 patients = 10.4% of all patients
- Nodule
  - Size 0.3-3.0 cm
- Patients with nodules were:
  - Age 8.5-18 yr

**US in Children with Goiter**
- 113 Korean patients < 20 yr old
- Nodules in 63.7%
  - 5.6% suspicious for malignancy
- Hypoechoogenicity
  - 88.5% of AIT
  - 85.7% of Graves’

**THYROID DISORDERS**
Hashimoto’s Thyroiditis
- Pathology: Extensive lymphocyte infiltration of gland
- Bossylated feel – difficult to feel nodules

**Thyroid Nodules in Poland Increased by 50% after suspension of iodine supplementation**
  - 411 Nodules
    - 358 (87.1%) girls
    - 53 (12.9%) boys
  - 5.2 / 100,000 children before 1996
  - 7.5 / 100,000 in 2000
  - Iodine supplementation suspended 1980-97

**Iodine Deficiency Increases Risk for Thyroid Nodules**
- NHANES III
- 6% children in US are Iodine deficient
  - All socioeconomic groups
  - Reduced use of iodized salt
  - Removal of iodine from
    - Baking
    - Milk
    - Red-dye

**1. What is the risk for malignancy in a nodule in a child?**
Pediatric Thyroid Nodules Higher Risk of Malignancy

Niedziela M. Pathogenesis, diagnosis and management of thy nod in children. Endo Related Cancer Volume 13, 427-53; 2006

TNM and Outcome in Children

- Multidisciplinary Working Group
  - Original articles, 97.5% DTC, > n=20
  - 8 retrospective cohorts n = 1,528
- Overall recurrence 14 - 49%

- Extrathyroidal extension and TNM predicted recurrence
  - Tumor size not a risk for recurrence
  - Some suggested lymph node metastases associated with recurrence but not all
  - Two studies showed distant metastases did not predict recurrence
  - Age and gender no relation to recurrence

- Conclude: Identifying children with lower TNM is of benefit but low quality of evidence

Clement et al. Cancer Treatment Reviews 2015; 41; 9-16

Query Radiation Exposure and Family History

- F HX benign thyroid disease 2.5-fold
- F Hx thyroid cancer 4.0-fold
- Familial non-medullary thyroid cancer 2-5% based on > 1 affected family member
- US should be done in childhood if family member has DTC


Serum TSH

- TSH<0.4
- 1.0-1.7
- >5.5

Probability

THEREFORE
Risk of Cancer is LOW (5%) with Suppressed TSH in Child

Boelaert et al, J Clin Endocrinol Metab 91:4295, 2006
Eszlinger et al Mol Cell Endocrinol 2014: 393(1-2) 39-45
Jatana and Zimmerman Otolaryngol Clin N Am 2015: 48(1) 47-58

HOWEVER
Most nodules are NOT HOT

Risk of Malignancy Increases with TSH

Bosnian et al, J Clin Endocrinol Metab 91:4295, 2006
Jatana and Zimmerman Otolaryngol Clin N Am 2015: 48(1) 47-58

Thyroid Ultrasound

- >103 nodules 74 confirmed with surgery
- >29 benign
- >35 malignant

Lyshchik A et al. Radiology 2005;235:604-613
Thyroid Nodules Predicting Malignancy

- 184 children and teens with nodule
  - 29 malignant, 8 FA, and 147 goitrous nodules
- US Features Associated with Malignant
  - Microcalcifications
  - Hypoechoic pattern
  - Intranodular vascularity
  - Abnormal lymph nodes
- TSH predicts malignancy
- Growth especially on L-T4 predicts malignancy

Mussa et al. J Pediatr 2015; S-0022-3476

Benign? Or Malignant?

Papillary Thyroid Carcinoma

Thyroiditis

- Scattered multiple hypoechoogenic micronodules and increased vascularity.


Thyroid Nodules in Children

- 300 children refer for new or suspected nodule
- 17 with low TSH and autonomous
- 283 refer for US
  - 46 subcentmieric nodules
  - 99 no discrete nodule
  - 9 non-thyroidal tumors
- 125 one or more nodule > 1 cm for FNA

Gupta et al. J Clin Endocrinol Metab 2013: 98(8) 3238-45

US Guided FNA
### Predicting Malignancy in Thyroid Nodules

- 184 children and teens with nodule
  - 29 malignant, 8 FA, and 147 goitrous nodules
- FNA
  - Accuracy 91%
  - Sensitivity 100%
  - Specificity 88%

### Comparison and Contrast Adult v Pediatric Guidelines

#### When to Perform FNA

**Pediatric**
- Size is problematic due to growth of gland (1 gm/yr of age)
- Size does not correlate with cancer risk in any study of nodules in children
- FNA for:
  - all nodules > 1 cm unless purely cystic
  - 0.5-1.0 cm if suspicious US
  - Small DTC more often look benign
  - M/PTC (23% pediatric FTC) or FTC often look benign

**Adult**
- FNA if nodule:
  - > 1 cm + intermediate or suspicious US
  - > 1.5 cm + low suspicion US
  - > 2 cm with very low suspicion US consider but not require FNA

#### Which Lesions Warrant FNA?

- Mussa et al. J Pediatr 2015; S-0022-3476

### Bethesda System for Reporting Thyroid Cytopathology

- (1) Nondiagnostic or unsatisfactory
- (2) Benign
- (3) Atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS)
- (4) Follicular/Hürthle neoplasm or suspicious for follicular/Hürthle neoplasm (FN or SFN)
- (5) Suspicious for malignancy (SUSP)
- (6) Malignant

### Comparison and Contrast Adult v Pediatric Guidelines

#### Bethesda Classification System Used For All Ages

<table>
<thead>
<tr>
<th>FNA</th>
<th>Pediatric (Overall DTC risk = 26%)</th>
<th>Adult (Overall DTC risk = 5-10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic</td>
<td><em>Usually benign</em></td>
<td>Nondiagnostic</td>
</tr>
<tr>
<td>Benign</td>
<td></td>
<td>Benign</td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>28%</td>
<td>AUS/FLUS</td>
</tr>
<tr>
<td>FN or suspicious for FN</td>
<td>&gt;58%</td>
<td>FN or suspicious for FN</td>
</tr>
<tr>
<td>Suspicious for CA</td>
<td>50%</td>
<td>Suspicious for CA</td>
</tr>
<tr>
<td>Malignant</td>
<td>100%</td>
<td>Malignant</td>
</tr>
</tbody>
</table>


### How to Follow Apparently Benign Nodules

**Pediatric**
- High suspicion US in children consider removal despite benign cytology (5% false neg)
- Low-intermediate suspicion repeat US at 12-24 months. Growth (no definition) or development of suspicious US warrants repeat FNA or removal
- ????

**Adult**
- High suspicion US repeat US and US-guided FNA within 12 months
- Low-intermediate suspicion US repeat US 12-24 months (50% increase volume or new suspicious features repeat FNA)
- Very low suspicion US no need for repeat US
- Benign FNA x 2 no follow up required

### Evolution of Care

**Child with thyroid Nodule:**

- **1980s**
  - essentially all nodules removed from children
- **1990s**
  - FNA to help identify cancer pre-op
  - BUT all children went to surgery
- **2015**
  - US features + FNA to identify cancer pre-op and allow pre-op staging
  - Benign nodules are expectantly observed if US and FNA benign
  - Possible genetic studies for AUS / FLUS
Pediatric Grand Rounds - UT Health San Antonio

Unifocal Thyroid Nodule (no radiation exposure)

Nuclear scintigraphy & treatment for thyrotoxicosis as indicated; surgery for functioning nodule(s) preferred

FNA under US guidance

Indeterminate (Follicular or Hürthle cell lesion/Neoplasm) or Suspicious

Inadequate or Non-diagnostic

Benign

Can consider LT4

Repeat US every 1-2 yrs.

Consider repeat FNA, for surgery

Repeat US every 3-6 mo.

Benign: Check adequacy of thyroid function in 4 wks & follow clinically

Malignant: PTC/MTC

Hemithyroidectomy (Consider intraoperative frozen section)

Can consider completion thyroidectomy & RAI vs. observation based upon final pathology

Indeterminate (Follicular or Hürthle cell lesion/Neoplasm) or Suspicious

Inadequate or Non-diagnostic

Benign

Can consider LT4

Repeat US every 6-12 mo.

Consider immediate repeat FNA or repeat US & FNA in 3-6mo. if clinical suspicion for cancer low

Malignant

How Common is DTC in Children?

Thyroid Cancer in Children

- 625 new cases in 2014
- 90% DTC
- 700 neuroblastoma
- 400 osteosarcoma
- 350 rhabdomyosarcoma


Suzuki et al. Fukushima Screening: Thyroid 2016; 26(6)843-851

US examination of 367,685 persons < 18 yr old

37.3 DTC / 100,000 = 1 / 2,680

Thyroid Cancer in Children

- 2001 - 2009
- All cancers together incidence stable
- Thyroid cancer increased 4.9% / yr
- Especially NE, S and Western US

Siegel et al. Pediatrics 2014; 134(4), e945-55

Is the increase due to detection of small lesions by imaging?

- If this was the explanation, mainly nonpalpable thyroid cancers would rise in incidence.
- Chen et al. found an increase in all stages in the SEER database
- Morris and Myssiorek found a 2-fold increase in large differentiated thyroid cancer (DTC) with extrathyroidal extension and cervical metastases

Chen et al. Cancer 2009; 115: 3801-3807
So Why Do Children Get DTC?

Thyroid Cancer in Children
- RET/PTC1 and RET/PTC3 = 80% of DTC
- Both increase
  - phosphorylation and over expression of EGF-R
- BRAF V600E 67% adult PTC, 31% Pediatric (p=0.03)
- 40% adult FTC PAX8/PPARγ

Hereditary PTC
- Utah Data Base
- 4,460 with PTC
  - First degree 5.4-fold
  - Second degree 2.2-fold
  - Third degree 1.8-fold
  - Increased risk for PTC
- Siblings had highest risk (6.8-fold)

CT Scan and Risk of DTC in Children
- 922 children and 971 CT scans
- Estimated thyroid dose
  - Paranasal sinus (0.61 - 0.92 mGy)
  - Head CT (1.1 – 2.45 mGy)
  - Chest CT (2.63 – 5.76 mGy)
- Lifetime risk

Evolution in Care Child with PTC:
- 1934
  - Schreiner and Murphy a “fatal disease with few exceptions”
- 1946
  - RAI used for DTC
- 1952
  - Puncture of thyroid (FNA)
- 1967
  - Ultrasound (US)
- 1980s
  - Total thyroidectomy no pre-op staging
  - “Berry-picking” suspicious lymph nodes
  - RAI ablation to “all” children
  - End-point = NED
- 2015
  - Total thyroidectomy after pre-op staging
  - Compartment focused lymph node dissection in most cases
  - Reserve RAI for “high-risk” children
  - End-point of therapy may not be NED for all children
Treatment for Children with Differentiated Thyroid Cancer

• Why did we move to this individualized approach?

• Previous treatment was easy……
• All children got TT, LN Dissection and RAI
• Why????

PTC — Children vs Adults

BUT WHAT WE LEARNED

• Therapy had high complication rate
• Disease-specific mortality is MUCH lower in children
  – Greater NIS expression
  – RAI sensitive
  – Microscopic pulmonary metastases
  – Different mutations (RET/PTC vs BRAF fusion gene)
  – Lack of progression to poorly differentiated tumors
  – ? more TSH dependent
  – ? more beneficial immunologic mechanisms

WHO NEEDS TT, LN dissection and RAI?
• Who can do just as well with less?
• What is a rational end-point for therapy?
• Do we need to achieve NED to have excellent survival?
• How can we tell if our therapy is working and how long will it work?
  – ie: Do we need annual RAI therapy?

Total Thyroidectomy Preferred for Most Cases

For the majority of children, total thyroidectomy is recommended.

RECOMMENDATION 11

Central Compartment (Level VI) Lymph Node Dissection


Cooper DS et al. Revised ATA Guidelines. Thyroid. Volume 19, Number 11; 2009
What About CND for PTC in Children and Adolescents?

- 83 consecutive cases < 18 yr
- 36 initial TT + CND (96%)
- Lateral neck in 57 patients ipsilateral (69%) and 35% contralateral
- 3 had no node dissection due to incidental PTC 4, 6 and 10 mm


PTC in Children and Adolescents

<table>
<thead>
<tr>
<th># nodes</th>
<th>0</th>
<th>1-10</th>
<th>11-20</th>
<th>&gt; 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Size</td>
<td>11-32 mm</td>
<td>16-33 mm</td>
<td>18-40 mm</td>
<td>19-35 mm</td>
</tr>
<tr>
<td>Multifocal</td>
<td>20%</td>
<td>14%</td>
<td>37%</td>
<td>90%</td>
</tr>
<tr>
<td>Extrathyroidal extension</td>
<td>10%</td>
<td>57%</td>
<td>61%</td>
<td>70%</td>
</tr>
<tr>
<td>Distant mets</td>
<td>0%</td>
<td>5%</td>
<td>11%</td>
<td>30%</td>
</tr>
<tr>
<td>Re-Operation</td>
<td>70%</td>
<td>48%</td>
<td>58%</td>
<td>59%</td>
</tr>
</tbody>
</table>

> 5 nodes = locoregional recurrence
> 70% of children had > 5 nodes
< TT increased recurrence by 10-fold
Incomplete node removal increased recurrence by 3-fold


Central Node Dissection and Complications

<table>
<thead>
<tr>
<th>Central Node Dissection</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laryngeal Nerve Palsy</td>
<td>0.01</td>
</tr>
<tr>
<td>Transient Hypopara</td>
<td>0.0001</td>
</tr>
<tr>
<td>Permanent Hypopara</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Machens et al. Surgery 2016. 160: 484-492

Can We Predict Central Node Metastases in Adults

- 209 PTC:
  - 158 node positive (N1) and 51 node negative (N0)
  - fvPTC
    - 7 / 158 N1 tumors (4.4%)
    - 24 / 51 N0 tumors (47.1%)
  - LNM more common in those with:
    - extracapsular extension
    - angiolymphatic invasion
    - T3 or T4 tumors
  - BRAF
    - more common in classic PTC than fvPTC
    - No relation to central nodes

RCT of Prophylactic Central Neck Dissection in Adult PTC

- 181 ADULTS PTC no pre or intra operative nodes
  - Random: 88 TT and 93 TT + pCND
  - 5 yr follow-up
- No Difference in outcomes
- HOWEVER
  - TT alone higher # of ¹³¹Iodine courses
  - TT+pCND higher permanent hypopara
- 50% had microscopic node disease not predicted by any pre-op feature including BRAF

Viola et al. J Clin Endocrinol Metab 2015: 100(4) 1316-24

ATA Pediatric Guidelines: Lymph Node Dissection

- RECOMMENDATION 12(A)
  - Central neck dissection (CND) is recommended for malignant cytology and clinical evidence of extra-thyroidal invasion or loco-regional metastasis
- RECOMMENDATION 12(B)
  - For PTC and no evidence of extra-thyroidal invasion or loco-regional metastasis, prophylactic CND may be selectively considered
- RECOMMENDATION 12(C)
  - Compartment-oriented resection is recommended. “Berry picking” and palpation are not recommended.

Viola et al. J Clin Endocrinol Metab 2015: 100(4) 1316-24

National Perspective Outcomes of DTC in Children

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical Nodes Present</td>
<td>14.7%</td>
<td>38.6%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lung Metastases</td>
<td>2.2%</td>
<td>5.7%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bone Metastases</td>
<td>1.1%</td>
<td>0.3%</td>
<td>= 0.04</td>
</tr>
<tr>
<td>Low-Volume Surgeon</td>
<td>16%</td>
<td>26.9%</td>
<td>= 0.005</td>
</tr>
<tr>
<td>Pediatric Surgeon</td>
<td>9.6%</td>
<td>14.5%</td>
<td>= 0.04</td>
</tr>
<tr>
<td>Low-Volume Hospital</td>
<td>15.2%</td>
<td>20.5%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Teaching Hospital</td>
<td>63.1%</td>
<td>81.7%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cost Excess Child Over Adult</td>
<td>$10,067.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications High Volume Surgeon</td>
<td>14.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications Low Volume Surgeon</td>
<td>35.9%</td>
<td>= 0.002</td>
<td></td>
</tr>
</tbody>
</table>

13¹I Therapy in Children Appears to Increase Disease Free Survival


Lack of Impact of Ablation on Nodal Recurrence in 161 PTC Patients <21 Yrs

**131I for PTC**

- Early Side Effects
  - Sialadenitis
  - Nausea, vomiting, diarrhea
  - Transient cytopenias
- Late side effects
  - Xerostomia/salivary calculi
  - Infertility (a concern for pubertal boys)
  - Pulmonary fibrosis/BM suppression
  - Malignancies—bladder, colon, breast, leukemias, salivary gland, stomach

**Risks of RAI Second Malignancy**

<table>
<thead>
<tr>
<th></th>
<th>No RAI</th>
<th>RAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.05</td>
<td>1.21</td>
</tr>
<tr>
<td></td>
<td>3.5/10,000 PY</td>
<td>13.3/10,000 PY</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.94</td>
<td>1.83</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1.07</td>
<td>2.48</td>
</tr>
</tbody>
</table>


**Childhood and Adolescent PTC**

Ian Hay, MD, Mayo Clinic

- Overall survival
  - Control: 75% at 60 yr
  - Thyroid Cancer: 60% at 60 yr
  - \( P = 0.001 \)
- Later deaths from non-thyroid cancer
  - 9 separate types of cancer
  - 5 / 13 had I-131
  - 6 / 13 received radium or radiation therapy
  - Only 2 / 13 (15%) never exposed to radiation

**9-year-old with PTC lung mets**

June 2003

April 2005

Cooper DS et al. Revised ATA Guidelines. Thyroid. Volume 19, Number 11; 2009

**Dosimetry for Significant Lung Disease**

**131I for DTC**

- Remnant Ablation
  - To facilitate detection of recurrent disease & initial staging
- Adjuvant Therapy
  - To decrease risk of recurrence & disease-specific mortality by destroying suspected, but unproven metastatic disease
- RAI Therapy
  - To treat known disease
ATA Pediatric DTC POST-OPERATIVE STAGING
Risk for Residual or Recurrent Disease

**NOT risk of death**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Definition</th>
<th>Initial Post-op Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Risk</td>
<td>Disease confined to the gland with N0/Nx disease OR incidental N1a</td>
<td>Tg</td>
</tr>
<tr>
<td>Intermediate-Risk</td>
<td>Extensive N1a disease or minimal N1b disease</td>
<td>TSH-stimulated Tg and diagnostic ¹²³I scan in most patients</td>
</tr>
<tr>
<td>High-Risk</td>
<td>Extensive N1b disease or invasive (T4) tumors, with or without distant mets</td>
<td>TSH-stimulated Tg and diagnostic ¹²³I scan in all patients</td>
</tr>
</tbody>
</table>

**ATA Pediatric Thyroid Cancer Risk Levels**

**AJCC TNM classification to describe extent of disease**

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td></td>
<td>≤ 1 cm, delimited to the thyroid</td>
</tr>
<tr>
<td>T2</td>
<td></td>
<td>&gt; 1 cm but ≤ 4 cm, delimited to the thyroid</td>
</tr>
<tr>
<td>T3</td>
<td></td>
<td>&gt; 4 cm, delimited to the thyroid, or any tumor with medullary or papillary invasion</td>
</tr>
<tr>
<td>T4</td>
<td></td>
<td>Any tumors, other tumors, other organs, or distant metastases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymph Node (N)</th>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td></td>
<td>Regional lymph node not detected</td>
</tr>
<tr>
<td>N1a</td>
<td></td>
<td>Metastases to regional lymph nodes, papillary, and medullary tumors</td>
</tr>
<tr>
<td>N1b</td>
<td></td>
<td>Metastases to regional lymph nodes, other tumors, other organs, and distant metastases</td>
</tr>
</tbody>
</table>

**Case**

- 6 yr 7 month male
  - Pea-sized swelling in the right lower neck
  - Observation was recommended by his pediatrician—continued to grow
- US showed evidence of metastatic lymphadenopathy and an abnormal thyroid
- FNA of LN was PTC
- No FH or other risk factors

**WHAT DO YOU DO NOW?**

**Initial Staging of PTC**

- Neck US (thyroid and lymph nodes)
- CT or MRI if bulky neck disease
- CXR or CT of chest if extensive neck disease
- What about FDG-PET?
- What about a nuclear medicine scan

**Ultrasound**

**Staging Chest X-ray**

- To identify macroscopic disease
  - Approach to RAI may change
- Will miss small lung mets but these usually picked up with RAI scan
- Consider CT if significant neck disease or if mets identified
**Thyroglobulin**

- Highly sensitive tumor marker for PTC
- Measure only once the Dx of PTC is established
- Always check anti-TG antibodies
  - Present in 25%
  - Precludes interpretation of TG levels
- Antibody levels may be followed, as cured patients are expected to normalize (3 yr)
- Stimulated TG levels are most sensitive but may sometimes be a false positive, esp. when <10

**Case: LABS**

- TSH 4.41 μU/ML (0.50-5.50)
- FT4 1.1 NG/DL (0.9-1.8)
- THYROGLOBULIN 393.0 NG/ML
- THYROGLOBULIN AB <20 IU/ML

**Factors Influencing the Basal and Recombinant Human Thyrotropin-Stimulated Serum Thyroglobulin in Patients with Metastatic Thyroid Carcinoma**


**TABLE 2. Serum Tg and sites of metastases in adults**

<table>
<thead>
<tr>
<th>Pure bone</th>
<th>Pure lung</th>
<th>Pure mediastinum</th>
<th>Pure cervical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-stimulated Tg (ng/ml) Median</td>
<td>48</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>MAXIMUM</td>
<td>65,400</td>
<td>1,190</td>
<td>120</td>
</tr>
<tr>
<td>Post-stimulated Tg (ng/ml) Median</td>
<td>416</td>
<td>72</td>
<td>16</td>
</tr>
</tbody>
</table>

**Case: CT**

for bulky or extensive neck disease

Small nodule seen in lung fields; CXR neg.

**Pathology**

- Multifocal PTC (follicular variant)—max 3.8 cm
- Extrathyroidal extension & lymphovascular invasion
- 4 / 8 level VI lymph nodes positive
- 11 / 48 levels II-V lymph nodes positive on R
- 8 / 32 levels II-V lymph nodes positive on R
- No tracheal or RLN involvement

**Initial Postsurgical Evaluation**

Diagnostic 131I scan:

Wt is 27.4 kg
TSH 119 μU/ml
TG 142 ng/ml (neg Ab)

Where is the uptake?
What Do You Do?
Case: Post-treatment SPECT-CT

Initial Postsurgical Evaluation

Diagnostic $^{131}$I scan:
Wt is 27.4 kg
TSH 119 μU/ml
TG 142 ng/ml (neg Ab)

What Do You Do?
60 mCi of $^{131}$I given

What If…?

Diagnostic $^{131}$I scan:
Wt is 27.4 kg
TSH 119 μU/ml
TG 142 ng/ml (neg Ab)

Would you treat?
Yes

What If…?

Diagnostic $^{131}$I scan:
Wt is 27.4 kg
TSH 119 μU/ml
TG 1.2 ng/ml (neg Ab)

Would you treat?
Probably Not

What If…?

Diagnostic $^{131}$I scan:
Wt is 27.4 kg
TSH 119 MCU/ml
TG 142 ng/ml (neg Ab)

Would you treat?
YES, with Surgery
• Who needs TT, LN dissection and RAI?
• Who can do just as well with less?

What is a rational end-point for therapy?
• Do we need to achieve NED to have excellent survival?
• How can we tell if our therapy is working and how long will it work? – ie: Do we need annual RAI therapy?

Prognosis relates to patient age, size of metastases, & RAI avidity

Cause-Specific Mortality in 215 PTC Patients Aged <21 Years

Cumulative occurrence (%)  
0% 0% 2% 2% 2% 2% 2%
10 20 30 40 50 Years after initial surgery

“Recurrence” rate as high as 30%

PTC in Children

• 227 PTC (7-20 yr old)
• 2 died of disease
• 45 recurrence  
  – (36 nodes, 7 remnant, 11 distant)
• Disease specific survival  
  – 10 yr = 99.3%, 20 yr = 99.3% and 30 yr = 96.5%
• DFS  
  – 10 yr = 83.6%, 20 yr = 70.7% and 30 yr = 64%

Sugino et al. World J Surg 2015; 39(9) 2259-65

Children with Pulmonary Metastases

• 21 patients 6-20 yr old  
  – Mean tumor 4.65 cm  
  – TT = 16, ST = 4, 20 some node dissection  
  – 19 RAI incremental doses until NED  
• Follow-up 21 yr (3 mo – 47 yr)  
• 9 / 21 recurrence

Brink et al. Br J Surg 2000; 87; 1256-78
Children with Pulmonary Metastases
• 39% recurrence risk at 5 yr
• 8 recur in cervical nodes
• NONE recur in lung
• 18 remain free from disease
• One recurrent node disease
• Two died; one of disease after 12 yr of multiple cervical relapse

Distant Metastasis in DTC
30 – 45% of children with pulmonary metastases
Develop stable but persistent disease
• 83 cases
  – 10 yr survival is 100%
  – Progression-free survival is 65 – 70% over 5 yr
• In Contrast to:
  – Adults with metastatic DTC
  – 50% - 5 yr survival
  – 30 – 40% - 10 yr survival
• They have persistent stable disease and
• Mortality is low
• How Much Disease Burden Can We Tolerate?

Distant Metastasis in DTC
• Persistent but non-progressive disease frequent
• generally 100% 10 yr survival
• Delayed responses to RAI can be seen:

Radiation Induced Injury
Time Line
• Immediate Effects
  – Membrane
  – Mitochondria
  – Cytokine release
  – Immediate cell death
• Bystander Damage
  – Blood vessels
  – Support stroma
• DNA damage
  – Repair enzymes
  – May survive until mitosis

Who needs TT, LN dissection and RAI?
• Who can do just as well with less?
• What is a rational end-point for therapy?
• Do we need to achieve NED to have excellent survival?
• How can we tell if our therapy is working and how long will it work?
  – is: Do we need annual RAI therapy?

ATa Pediatric Thyroid Cancer Recurrence Risk

<table>
<thead>
<tr>
<th>Initial TSH Goal</th>
<th>Surveillance of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-Risk</strong></td>
<td>0.5-1.0 mIU/L</td>
</tr>
<tr>
<td><strong>Intermediate-Risk</strong></td>
<td>0.1-0.5 mIU/L</td>
</tr>
<tr>
<td><strong>High-Risk</strong></td>
<td>&lt; 0.1 mIU/L</td>
</tr>
</tbody>
</table>
Thyroid Cancer in Children

- Review 1,800 DTC in children
- Suggest:
  - in well-operated low-risk patients stimulated Tg post op and diagnostic RAI scan
  - if NEG defer RAI therapy
- TSH suppression < 0.1 mU/L in high risk
  - and < 0.5 mU/L after remission
- Undetectable Tg = no action
- Tg < 2 ug/L = neck US
- Tg > 10 = neck US and if neg
  - then neck MR or chest CT
- Surgery if possible
- RAI in distant pulmonary metastases


ATA Guideline for Children

- Low-level TSH-stimulated Tg (<10 ng/ml) in a patient who has undergone surgery and therapeutic 131I may indicate disease. This may decline without additional therapy.
  - Continued follow up is indicated.
- Increasing or TSH-stimulated Tg > 10 ng/ml warrants further evaluation to localize disease and decide if surgery and/or 131I would benefit. Or consider continued observation.

Francis et al. Thyroid 2015; 25:716-759

2015 ADULT
ATA Re-Staging Classification
Haugen et al Thyroid 2016. 26(1) 1-133

<table>
<thead>
<tr>
<th>Response</th>
<th>Imaging</th>
<th>Suppressed Tg</th>
<th>TSH-Stimulated Tg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent Response (ER)</td>
<td>Negative</td>
<td>&lt; 0.2 ng/ml</td>
<td>&lt; 1 ng/ml</td>
</tr>
<tr>
<td>Indeterminate Response (IR)</td>
<td>Non-Specific bed</td>
<td>&lt; 1.0 ng/ml</td>
<td>&lt;10 ng/ml</td>
</tr>
<tr>
<td>Biochemical Incomplete Response (BIR)</td>
<td>Negative</td>
<td>≥ 1.0 ng/ml</td>
<td>≥ 10 ng/ml</td>
</tr>
<tr>
<td>Structural Incomplete Response (SIR)</td>
<td>Positive</td>
<td>any</td>
<td>any</td>
</tr>
</tbody>
</table>

ADULT Pre-Ablation TSH-Stimulated Tg
Yang et al. J Clin Endocrinol Metab 2016. 101(3) 1307-1313

<table>
<thead>
<tr>
<th>Tg (ng/ml)</th>
<th>ER (n=203)</th>
<th>IDR (n=92)</th>
<th>BIR (n=70)</th>
<th>SIR (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>92.68%</td>
<td>7.32%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1-10</td>
<td>58.96%</td>
<td>31.79%</td>
<td>7.52%</td>
<td>1.73%</td>
</tr>
<tr>
<td>≥ 10</td>
<td>12.69%</td>
<td>15.74%</td>
<td>28.93%</td>
<td>42.64%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Ps-Tg (ng/ml)</th>
<th>Quartiles (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>1.9</td>
</tr>
<tr>
<td>IDR</td>
<td>6.44</td>
</tr>
<tr>
<td>BIR</td>
<td>24.55</td>
</tr>
<tr>
<td>SIR</td>
<td>226.5</td>
</tr>
</tbody>
</table>

Case 2

- 17 year old female
- Thyroiditis since age 8 yr
- Palpable thyroid mass
- PE: 2.3 cm right lobe mass; no palpable neck LNs

Case #2

TSH: 0.57 μU/ml, fT4 1.4 ng/dl
Ultrasound:
Well-circumscribed isoechoic nodule with hypoechogenic margins 1.91 cm x 1.72 cm x 1.71 cm increased color flow. No calcifications. No enlarged lymph nodes.
Case #2: FNA

High cellularity
Disorganized flat sheets, complex follicular groups, tubular arrangements and scattered microfollicles

Cells with moderate amount of cytoplasm, crowded, overlapping ovoid nuclei with irregular contours and small nucleoli.

Scattered nuclear grooves.
No pseudoinclusions are identified despite extensive search.

Background shows abundant blood, fragments of thick colloid and few very large multinucleated giant cells.

**Suspicious for Follicular Neoplasm**

---

**Case 2, Questions**

- What is the differential diagnosis and the risk of malignancy?
- What tests should be done?
- What should be done now?

<table>
<thead>
<tr>
<th>FNA</th>
<th>Cancer Risk (Limited Data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic</td>
<td>“Usually benign”</td>
</tr>
<tr>
<td>Benign</td>
<td>5%</td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>28%</td>
</tr>
<tr>
<td>FN or suspicious for FN</td>
<td>&gt;58%</td>
</tr>
<tr>
<td>Suspicious for CA</td>
<td>100%</td>
</tr>
<tr>
<td>Malignant</td>
<td>100%</td>
</tr>
</tbody>
</table>

---

**FTC**

- FTC uncommon (10%) in children
- Cannot be distinguished from follicular adenoma by FNAB
  - Dx requires pathology to show vascular or capsular invasion
- ALL follicular neoplasms should be removed (Lobectomy)

Molecular studies designed for FTC
many FTC have mutations not detected by current molecular screens
No molecular studies may not be helpful
Absence of mutations still has moderate malignant risk

---

**FTC**

- FTC spreads by hematogenous routes
  - Not lymphatics like PTC
- RAI is recommended for all but FTC with minimal invasion
- Recent study:
  - 20 children with FTC
    - 16 minimally invasive
    - 4 widely invasive tumors
    - vascular or lymphatic invasion was seen in 9 / 20
- Recurrence in 3
  - all were minimally invasive, but 3 had vascular invasion
  - Suggests minimally invasive FTC with vascular invasion might require more aggressive therapy
- 30 year disease-specific survival 100% and disease-free survival 62.8%

---

• Total thyroidectomy
  – 4 cm tumor with extrathyroidal extension
• Central compartment node dissection
  – 47 / 123 nodes positive several through capsule
• RAI therapy
  – 136 mCi 131-Iodine

Follow-Up

<table>
<thead>
<tr>
<th>Date</th>
<th>2/10/16</th>
<th>5/27/16</th>
<th>9/23/16</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (uIU/ml)</td>
<td>0.41</td>
<td>61</td>
<td>0.15</td>
</tr>
<tr>
<td>Tg (ng/ml)</td>
<td>184</td>
<td>1006</td>
<td>207</td>
</tr>
</tbody>
</table>

Persistent elevation in serum Tg
No uptake in lung lesions

Is this RAI refractory disease
Is RAI going to have an effect if we wait

7-Day Post-Therapy Scan
2.3% neck uptake
Nothing in lungs

Comparison and Contrast Adult v Pediatric Guidelines
RAI Refractory Disease

<table>
<thead>
<tr>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Definition of RAI Refractory Disease</td>
<td>Tumor never takes up RAI</td>
</tr>
<tr>
<td>Tumor loses RAI uptake</td>
<td>RAI uptake in some but not all lesions</td>
</tr>
<tr>
<td>Mets progress despite RAI uptake</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1.7 Composite showing ordered views of uptake activity. PTC - Long bones.
Iodine 131 Heterogeneity in absorbed dose distribution in individual patient PET 124 Iodine

RAI-Refractory Disease
- Not all RAI-refractory recurrence progresses
- Not all RAI-refractory recurrence is immediate threat to life
- 74 DTC
  - 8 - 82 yr old with RAI-refractory mets
- 5 and 10 yr cause-specific survival
  - was 95% and 70%

DEFINING RAI REFRACTORY THYROID CANCER: WHEN IS RAI THERAPY UNLIKELY TO ACHIEVE A THERAPEUTIC RESPONSE?
R Michael Tuttle, MD and Mona M. Sabra, MD
Endocrinology Service, Memorial Sloan-Kettering Cancer Center, New York, New York, 10021

RAI-Refractory Disease
- Not all RAI-refractory recurrence progresses
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- 74 DTC
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- 5 and 10 yr cause-specific survival
  - was 95% and 70%

Ito et al. Endocr J 2014: 61(8) 821-824

Comparison and Contrast Adult v Pediatric Guidelines
Therapy for RAI Refractory Disease

Pediatric
- Molecular therapies may be contemplated for the rare child who needs systemic treatment.
- Hard to define iodine-refractory DTC and it may remain stable over years in children.
- All children for anti-neoplastic therapy should be sent to centers familiar with the use of these novel therapeutic agents in thyroid cancer.

Adult
- Asymptomatic stable
  - Follow on TSH suppression
  - Isolated brain, lung, liver, bone
  - Stereotactic radiation or thermal
- SYMPTOMATIC PROGRESSIVE
  - not amenable to other therapies
  - Kinase inhibitors may be considered

Sorafenib in iodine refractory thyroid cancer double blind placebo controlled
- Sorafenib 400 mg PO BID
  - > 18 yr old, progression in 12 months prior
  - TSH < 0.5 mIU/L
- Intention to treat 207 sorafenib 210 placebo
- Median progression free survival
  - 10.8 vs 5.8 months regardless of BRAF or RAS mutations
- 98.6% AE vs 87.6% placebo
  - Hand-foot syndrome (76.3%)
  - diarrhea (68.6%)
  - alopecia (67.1%)

Gori et al. Tumori 2013: 99(6) 285e-7e

Selumetinib increases RAI uptake in RAI-Resistant TC
- MAPK kinase (MEK 1 and MEK2) inhibitor selumetinib in patients with metastatic TC.
- After stimulation with thyrotropin
  - Dosimetry with iodine-124 positron-emission tomography (PET)
  - Before and 4 weeks after treatment with selumetinib
  - (75 mg twice daily)
- N = 20: median age 61 years (range, 44 to 77) No Children
  - Nine patients had BRAF mutations
  - 5 patients had mutations of NRAS


Selumetinib increases RAI uptake in RAI-Resistant TC
- Selumetinib increased the uptake of iodine-124
  - 12 / 20 patients
  - 4 of 2 patients with BRAF mutations
  - 5 of 5 patients with NRAS mutations
- 8 / 12 reached dosimetry threshold for RAI therapy
  - including all 5 with NRAS mutations.
- Of the 8 patients treated with RAI
  - 5 had partial responses
  - 3 had stable disease
  - all patients had decreases in serum Tg levels (mean -89%)
- No SAE grade 3 or higher attributable to selumetinib

Thanks for Your Attention!!!

- Remember:
  - Thyroid nodules and cancers are common in children
  - Second most common presentation in children is persistent cervical adenopathy
  - 40% are discovered by parent
  - Radiation exposure increases the risk but IS NOT REQUIRED